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(73) Proprietor: **JOHN WYETH & BROTHER LIMITED**
Huntercombe Lane South
Taplow
Maidenhead Berkshire, SL6 0PH (GB)

(72) Inventor: **Cliffe, Ian Anthony**
14 St Andrews Way
Cippenham, Slough, Berkshire (GB)
Inventor: **Mansell, Howard Langham**
142 Lent Green Lane
Burnham, Buckinghamshire (GB)

(74) Representative: **Brown, Keith John Symons et al**
c/o Wyeth Laboratories
Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 0PH. (GB)

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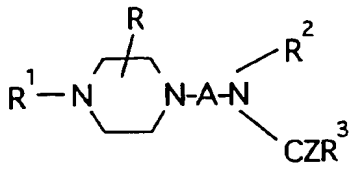
This invention relates to piperazine derivatives, to processes for their preparation, to their use and to pharmaceutical compositions containing them. The novel compounds act on the central nervous system by binding to 5-HT receptors (as more fully explained below) and hence can be used as medicaments for treating humans and other mammals.

EP-A-0372657 discloses a group of 1,4-disubstituted piperazine derivatives which are stated to have psychotropic properties.

The novel compounds of the invention are those of the general formula



(I)

and the pharmaceutically acceptable acid addition salts thereof.

In formula (I)

A is an alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,

Z is oxygen or sulphur,

R is hydrogen or lower alkyl,

R^1 is a mono or bicyclic aryl or heteroaryl radical,

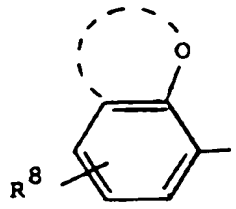
R^2 is a mono or bicyclic heteroaryl radical

and R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl(lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, COaryl, aryl(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom] or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl-(lower)alkyl].

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. Preferably such radicals contain 1 to 4 carbon atoms. Examples of "lower alkyl" radicals are methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, pentyl and isopentyl.

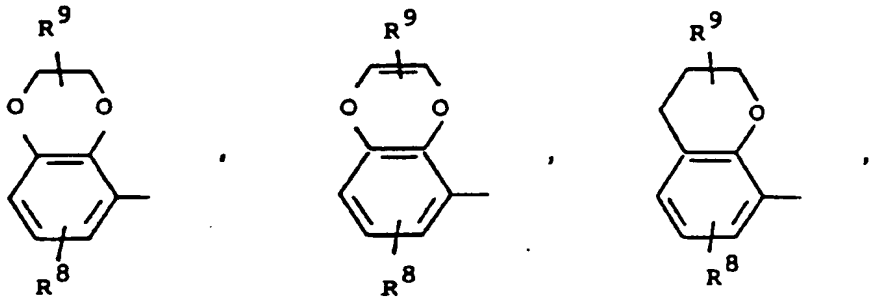
Examples of cycloalkyl groups are cyclopentyl, cyclohexyl and cycloheptyl. A preferred example is cyclohexyl. Cycloalkyl groups include bicyclic, tricyclic and tetracyclic groups, eg adamantyl. Preferably the cycloalkyl group contains 3 to 12 carbon atoms.

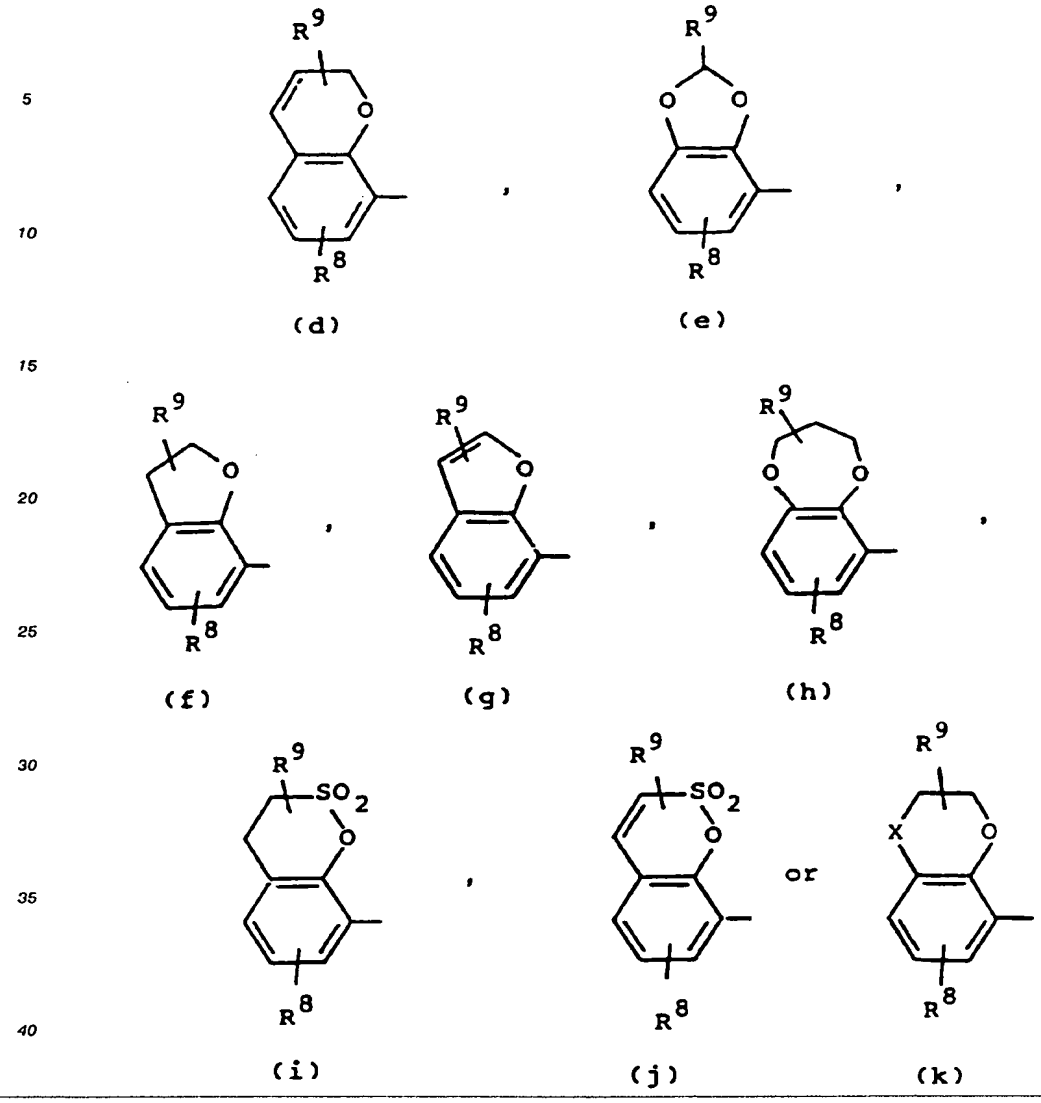
When used herein "aryl" means an aromatic radical having 6 to 12 carbon atoms (eg phenyl or naphthyl) which optionally may be substituted by one or more substituents. Preferred substituents are lower alkyl, lower alkoxy (eg methoxy, ethoxy, propoxy, butoxy), halogen, halo(lower)alkyl (eg trifluoromethyl), nitro, nitrile, amido, (lower)alkoxycarbonyl, amino, (lower)alkylamino or di(lower)alkylamino substituents. Two substituents on the aromatic ring may be connected together to form another ring system. For example R^1 may be an optionally substituted tetrahydronaphthyl radical or a bicyclic oxygen-containing radical of the formula



wherein the heterocyclic ring containing the oxygen atom contains a total of 5 to 7 ring members, said heterocyclic ring being saturated or unsaturated, being optionally substituted and optionally containing one or more hetero ring members (eg -O-, NR^7 - where R^7 is hydrogen or lower alkyl, -S- or $-SO_2-$) in addition to the oxygen atom illustrated and wherein R^8 represents hydrogen or one or more same or different substituents selected from lower alkyl, halogen, oxo, hydroxy, (lower)alkoxy, hydroxy(lower)alkyl, (lower)-alkoxy(lower alkyl), lower alkanoyloxy(lower alkyl), (lower)alkylcarbonyl, (lower)alkylcarbonyl(lower)alkyl, amino, (lower)alkylamino or di(lower)alkylamino.

Preferred examples of a bicyclic oxygen-containing radical are those of the formulae





where R^8 is as defined above, R^9 has the definition of R^8 given above and X is -CO-, -S-, or $-NR^7-$ where R^7 is hydrogen or lower alkyl.

When R^1 is an aryl radical it is preferably a phenyl radical containing a substituent in the ortho position. A preferred example of R^1 is o-(lower)alkoxyphenyl eg o-methoxyphenyl. R^1 can also be, for example a 1-naphthyl radical optionally substituted in the 2 or 7 positions by, for example, (lower)alkoxy.

Preferred examples of aryl(lower)alkyl are benzyl and phenethyl in which the phenyl rings may be substituted by substituents as given above.

The term "heteroaryl" refers to an aromatic radical containing one or more hetero atoms (eg oxygen, nitrogen, sulphur) and which may be optionally substituted by one or more substituents. Examples of suitable substituents are given above in connection with "aryl" radicals. The heteroaryl radical may, for example, contain up to 10 ring atoms. Preferably the heteroaryl radical is a monocyclic radical containing 5 to 7 ring atoms. Preferably the hetero ring contains a nitrogen hetero atom with or without one or more further hetero atoms. When R^1 is a heteroaryl radical it is preferably an optionally substituted pyrimidyl (particularly 2-pyrimidyl), isoquinolinyl (particularly 1-isoquinolinyl) or 1,2-benzisothiazolyl radical. When R^2

is a bicyclic heteroaryl radical both rings of the radical may contain hetero ring atoms or only one ring may contain a hetero atom or atoms. In the latter instance the radical R^2 is connected to the rest of the molecule of formula (I) via the ring containing the hetero atom(s).

Examples of the heteroaryl radical R^2 include monocyclic radicals containing one hetero atom, eg optionally substituted pyridyl (particularly 2-pyridyl), monocyclic radicals containing two hetero atoms, eg thiazolyl (particularly 2-thiazolyl) and bicyclic radicals containing one or two hetero atoms eg quinolinyl or isoquinolinyl (particularly 2-quinolinyl).

When R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring this may be, for example, azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino which may be optionally substituted by, for example, lower alkyl, aryl or aryl(lower)alkyl.

Preferred compounds have the following substituents either independently or in combination:-

(a) A is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-CH(CH_3).CH_2-$

(b) R is hydrogen

(c) R^1 is o-methoxyphenyl, o-isopropylphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dihydro[1,4]benzodioxan-5-yl), pyrimid-2-yl, 1-naphthyl,3-(1,2-benzisothiazolyl), 1-(7-methoxynapthyl) or 1-(5,6,7,8)-tetrahydronaphthyl

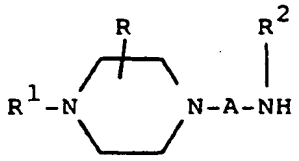
(d) R^2 is pyrid-2-yl, quinolin-2-yl or thiazol-2-yl

(e) R^3 is lower alkyl (eg methyl or t-butyl), cycloalkyl (eg cyclohexyl), cycloalkenyl (eg cyclohexenyl), phenyl, piperidino, adamantyl, or -NHcycloalkyl (eg -NHcyclohexyl)

(f) Z is oxygen

The compounds of the invention may be prepared by methods known in the art from known starting materials or starting materials that may be prepared by conventional methods.

One method of preparing the compounds of the invention comprises acylating an amine of formula



(II)

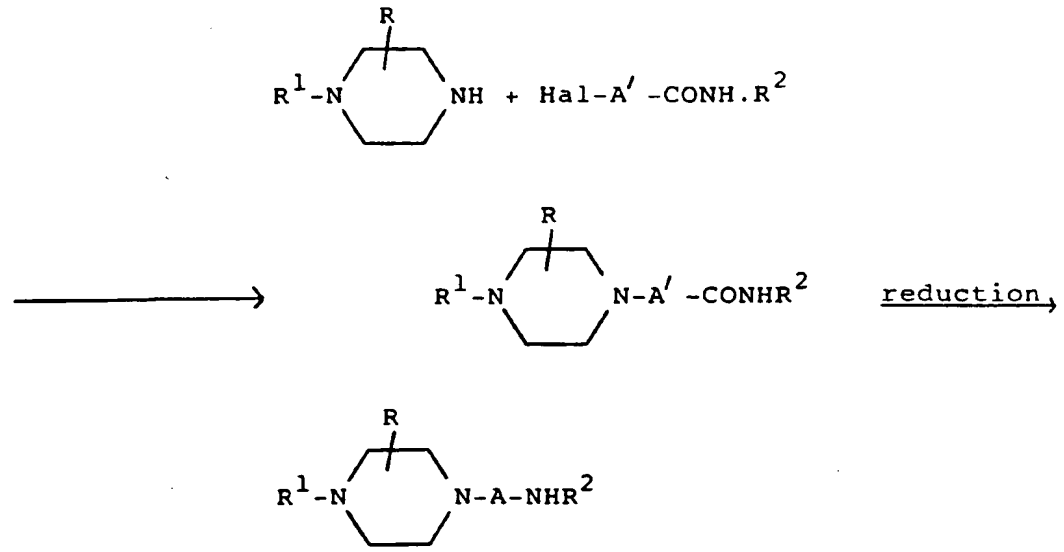
(where A, R, R^1 and R^2 have the meanings given above) with an acid of formula

R^3CZOH (III)

(where Z and R^3 is as defined above) or with an acylating derivative thereof. Z is preferably oxygen. Examples of acylating derivatives include the acid halides (eg acid chlorides), azides, anhydrides, imidazolides (eg obtained from carbonyldiimidazole), activated esters or O-acyl ureas obtained from a carbodiimide such as a dialkylcarbodiimide particularly cyclohexylcarbodiimide.

Compounds in which R^3 is $-NR^4R^5$ are urea or thiourea derivatives and may be prepared by reacting an amine of formula (II) with the appropriate isocyanate or isothiocyanate (including an appropriate acylisocyanate or acylisothiocyanate). Ureas in which R^5 is -CO(lower)alkyl or -CO aryl may also be prepared by acylating the corresponding urea or thiourea in which R^5 is hydrogen.

The starting amine of formula (II) may be prepared by a process such as that exemplified below:



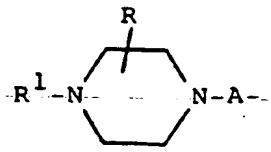
(where R, R^1, R^2 and A are as defined above, Hal is halo, particularly chloro or bromo and A' is an alkylene chain of 1 to 3 carbon atoms optionally substituted by one or more lower alkyl groups). The reduction may be carried out with, for example, a boron reducing agent eg borane-dimethyl sulphide or a complex metal hydride, eg lithium aluminium hydride.

Some of the amines of formula (II) are novel. A particularly preferred novel amine, which is provided by the present invention is 1-(2-methoxyphenyl)-4-[2-(2-pyridinylamino)ethyl]-piperazine.

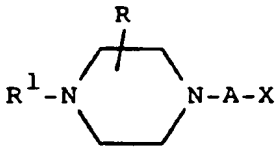
A further method of preparing the compounds of the invention comprises alkylating an amide or thioamide of formula (IV)

(IV)

with an alkylating agent providing the group

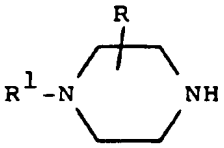


The alkylating agent may be, for example, a compound of formula



where A, R and R^1 are as defined above and X is a leaving group such as halogen or an alkyl - or aryl-sulphonyloxy group. Z is preferably oxygen.

A further method of preparing the compounds of the invention comprises alkylating a compound of formula



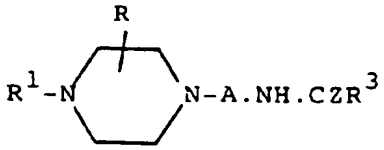
with a compound of formula

$X\text{-}A\ NR^2.CZ.R^3$ (V)

(where A, R, R^1, R^2, R^3, Z and X are as defined above). Z is preferably oxygen. The starting compound of formula (V) may, for example, be prepared as exemplified below

$X\text{-}A\text{-}Br + NHR^2CZR^3$ (V)

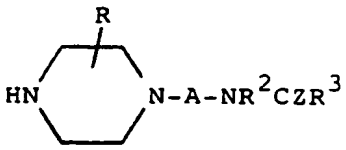
A further method of preparing the compounds of the invention comprises heteroarylating a compound of formula



(VI)

with a compound providing the heteroaryl group R^2. For example the compound of formula (VI) may be reacted with a fluoro compound of formula R^2F eg in the presence of a strong non-nucleophilic base (eg lithium diisopropylamide).

Where R^1 is a group that is activated towards nucleophilic substitution the compounds of the invention may be prepared by a further method which comprises reacting the appropriate fluoro compound of formula R^1F with a piperazine compound of formula



Compounds of the invention in which Z is sulphur may be prepared by sulphurisation of compounds of the invention where Z is oxygen. The compounds where Z is oxygen may, for example, be reacted with a sulphurising agent such as a mixture of phosphorus pentasulphide and potassium sulphide.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic, p-toluenesulphonic, oxalic and succinic acids.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that some compounds can exist in different steroisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

The compounds of the present invention possess pharmacological activity. In particular, they act on the central nervous system by binding to 5-HT receptors. In pharmacological testing it has been shown that the compounds particularly bind to receptors of the 5-HT_{1A} type. In general, the compounds selectively bind to receptors of the 5-HT_{1A} type to a much greater extent than they bind to other receptors such as α_1 and D_2 receptors. Many exhibit activity as 5-HT_{1A} antagonists in pharmacological testing. The compounds of the invention can be used for the treatment of CNS disorders, such as anxiety in mammals, particularly humans. They may also be used as antidepressants, hypotensives and as agents for regulating the sleep/wake cycle, feeding behaviour and/or sexual function.

The compounds of the invention were tested for 5-HT_{1A} receptor binding activity in rat hippocampal membrane homogenate by the method of B S Alexander and M D Wood, J Pharm Pharmacol, 1988, 40, 888-891.

The compounds of Examples 3, 4, and 17, which are representative compounds of the invention, had IC_{50}'s of respectively 2.2, 5.8 and 3 nM in this test procedure.

The compounds are tested for 5-HT_{1A} receptor antagonism activity in a test involving the antagonism of 5-carboxamidotryptamine in the guinea-pig ileum in vitro (based upon the procedure of Fozard et al, Br J Pharmac, 1985, 86, 601P). The results for representative compounds of the invention are given below. The compound of Example 3 had a pA_2 of 8.7 and that of Example 4 had a pA_2 of 7.8 and that of Example 17 had a PA_2 of 9.8.

The invention also provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

Solid form compositions include powders, granules, tablets, capsules (eg hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aides, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, eg from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable exampl s of liquid carriers for oral and parenteral administration include water (particularly containing additives as above,

eg cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols, eg glycerol and glycols) and their derivatives, and oils (eg fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, eg as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged composition, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The following Examples illustrate the invention. Examples 1,2,7,9,10,12-16,18,19,21-29,32 and 34-45 illustrate the preparation of intermediates and these intermediates, apart from the intermediate of Example 2, are not claimed in the present specification. The compound of Example 2 is provided by the present invention.

Example 1

2-(1-(4-(2-Methoxyphenyl)piperazinyl))-N-(2-pyridinyl)acetamide

A stirred solution of 2-chloro-N-(2-pyridinyl)acetamide (9.9g, 58 mmol) in dry DMF (40 ml) at 0 °C was treated with 1-(2-methoxyphenyl)piperazine (11.1g 58 mmol) in dry DMF (40 ml), treated with potassium carbonate (9.2g, 67 mmol), after 30 min warmed to room temperature and after 18h treated with water (400 ml). The emulsion was extracted with ether (3 x 200 ml) and the extracts washed with water (500 ml), dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. Purification by chromatography (silica; ethyl acetate) gave the product (17.3g) as an oil which crystallised on standing, m.p. 86-89 °C.

Example 2

1-(2-Methoxyphenyl)-4-(2-(2-pyridinylamino)ethyl)piperazine

A solution of the product of Example 1 (13.87g, 42.5 mmol) in THF (150 ml) was heated under reflux under Ar, treated dropwise with borane-dimethyl sulphide (8 ml, 84.3 mmol), after 2½ h treated dropwise with methanol (50 ml) and treated with ¼N-HCl (200 ml). After 1 hr the reaction mixture was cooled to room temperature, washed with ethyl acetate (2 x 200 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were dried (Na_2SO_4) and evaporated in vacuo to give the product as an oil (11.8g). The product was purified by chromatography [silica, ethyl acetate-ethanol (20:1)] and converted to the salt-form with ethereal-hydrogen chloride. Crystallisation from acetonitrile gave the trihydrochloride salt of the product as white crystals, m.p. 212-214 °C.
(Found: C, 50.8; H, 6.7; N, 13.2 $C_{18}H_{24}N_4O.3HCl.\frac{1}{4}H_2O$ requires C, 50.7; H, 6.5; N, 13.1%).

Example 3

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

A stirred suspension of potassium hydride, 35 wt.% suspension in mineral oil (2.99g, ca. 26.1 mmol) in DMF (25 ml) was treated dropwise under Ar with the free base of Example 2 (2.14g, 6.9 mmol) in DMF (15 ml). The reaction mixture was treated dropwise after 20 min with cyclohexanecarbonyl chloride (1.4 ml, 10.5 mmol), and after 1 hr treated carefully with water (200 ml), acidified with 2N-HCl (ca. 70 ml), washed with hexane (2 x 200 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were washed with brine (100 ml), dried (Na_2SO_4), and evaporated in vacuo to give a red oil which was purified by chromatography (silica; ethyl acetate). A solution of the oil in methanol (40 ml) was acidified with ethereal hydrogen chloride and evaporated in vacuo to give the trihydrochloride salt of the product (1.04g), m.p. 165-172 °C (dec.)

(Found: C, 54.2; H, 7.3; N, 10.0% $C_{25}H_{34}N_4O_2.3HCl.H_20$ requires C, 54.6; H, 7.15; N 10.2%).

Example 4

N-Cyclohexyl-N'-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)urea

A stirred suspension of potassium hydride, 35 wt. % suspension in mineral oil (2.91g, ca. 21.8 mmol) in dry DMF (20 ml) was treated dropwise with the free base of Example 2 (2.92 g, 9.4 mmol) in dry DMF (15 ml) under Ar. After 1 h the reaction mixture was treated with cyclohexyl isocyanate (1.3 ml, 10.2 mmol) and after a further 18 h treated with water (200 ml), acidified with 2N-HCl (ca. 50 ml), washed with hexane (2 x 200 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were washed with brine (200 ml), dried (Na_2SO_4), and evaporated in vacuo to give a brown oil which was purified by chromatography (silica; ethyl acetate, then alumina; ether). The colourless oil was dissolved in ethanol (10 ml) and the solution acidified with ethereal hydrogen chloride and evaporated in vacuo to give the trihydrochloride salt of the product as a hydrated glass containing a quarter mole of ethyl acetate (0.456g) (Found: C, 53.2; H, 7.5; N, 11.8. $C_{25}H_{35}N_5O_2.3HCl.H_2O.\ \frac{1}{4}C_4H_8O_2$ requires C, 53.2; H, 7.2; N, 11.9%).

Example 5

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)benzamide

Benzoyl chloride (1.69g, 12 mmol) was added cautiously to a stirred solution of Example 2 free base (1.94g, 6 mmol) and di-isopropylethylamine (2.2 ml, 14 mmol) in dichloromethane (20 ml). The mixture was stirred under Ar for 24 h, evaporated in vacuo, and the brown oil dissolved in water (50 ml). The solution was acidified with 2N-HCl, washed with dichloromethane (3 x 50 ml), basified with 2N-NaOH, and extracted with dichloromethane (3 x 75 ml). The extracts were dried ($MgSO_4$), evaporated in vacuo, and the residue purified by chromatography [alumina; toluene-ethyl acetate (7:3)]. The oil was dissolved in ethyl acetate (10 ml) and the dihydrochloride salt of the product precipitated with ethereal hydrogen chloride as colourless crystals (1.3g), m.p. 105-112 °C
(Found: C, 61.6; H, 6.1; N, 11.3. $C_{25}H_{28}N_4O_2.2HCl$ requires C, 61.4; H, 6.2; N, 11.5%).

Example 6

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)trimethylacetamide

This compound was synthesised by an analogous method to that used for Example 5, substituting trimethylacetyl chloride (1.57g, 13 mmol) for benzoyl chloride, to give the trihydrochloride salt of the product (1.2g) as a white solid, m.p. 138-140 °C
(Found: C, 53.5; H, 7.3; N, 10.8. $C_{23}H_{32}N_4O_2.3HCl.\frac{1}{2}H_2O$ requires C, 53.7; H, 7.1; N, 10.9%).

Example 7

N-(2-thiazolyl)cyclohexanecarboxamide

Cyclohexanecarbonyl chloride (4.38g, 30 mmol) was added dropwise to a solution of 2-aminothiazole (3.00g, 30 mmol) and di-isopropylethylamine (3.87g, 30 mmol) in dichloromethane (50 ml) at 0 °C. The mixture was warmed to room temperature, stirred for 18 h, washed with 1 N-HCl (2 x 50 ml) and 1 N-NaOH (2 x 50 ml), dried ($MgSO_4$), and evaporated in vacuo to give the product (4.59g) as white crystals.

Example 8

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-thiazolyl)cyclohexanecarboxamide

A solution of the product of Example 7 (2.10g, 10 mmol) in DMF was added dropwise to a stirred suspension of potassium hydride, 35 wt. % suspension in mineral oil (1.6g, ca 14 mmol) in DMF (20 ml) under Ar. After 1 h, 1-(2-chloroethyl)-4-(2-methoxyphenyl)piperazin (2.53g, 10 mmol) was added portion-wise and the mixture stirred at 80 °C for 5 h. Saturated aq. Na_2CO_3 (20 ml) was added cautiously and the mixture concentrated in vacuo. The residue was taken up into ether (100 ml) and extracted with 1N-HCl (3 x

50 ml). The aqueous phases were basified with 1N-NaOH and xtracted with ether (3 x 50 ml). Th ethereal extracts were dried ($MgSO_4$), evaporated in vacuo, and the residue purified by chromatography (silica; ethyl acetate). The oil was dissolved in ethyl acetate (10 ml) and the dihydrochloride salt of the product precipitated with ethereal hydrogen chloride as a white solid (1.1g), m.p. 205 • C (a phase change was observed at 80 • C and the sample decomposed at 205 • C).
(Found: C, 53.4: H, 6.8: N, 10.7. $C_{23}H_{32}N_4O_2S$ 2HCl.¾ H_2O requires C, 53.6; H, 7.0; N, 10.9%).

Example 9

2-(1-(4-(4-Fluoro-2-methoxyphenyl)piperazinyl))-N-(2-pyridinyl)acetamide

A stirred solution of 2-chloro-N-(2-pyridinyl)acetamide (0.94g, 5.5 mmol) in dry DMF (10 ml) was treated with 1-(4-fluoro-2-methoxyphenyl)piperazine (1.16g, 5.5 mmol) and di-isopropylethylamine (1.1 ml, 6.3 mmol), and after 19h treated with water (50 ml). The emulsion was extracted with ether (2 x 50 ml) and the extracts washed with water (100 ml), dried
($MgSO_4$) and evaporated in vacuo to give a yellow oil. Purification by chromatography (silica; ether) gave the product (1.61g) as colourless crystals, m.p. 110-120 • C (sample softens at 32 • C).

Example 10

1-(4-Fluoro-2-methoxyphenyl)-4-(2-(2-pyridinylamino)ethyl)piperazine

A solution of the product of Example 9 (1.51g, 4.4 mmol) in THF (20 ml) was heated under reflux under Ar and treated dropwise with borane-methyl sulphide complex, 2M solution in THF (4.4 ml, 8.8 mmol). After 4 h the reaction mixture was treated dropwise with methanol (10 ml) and treated with 2N-HCl (10 ml). After 1 hr the reaction mixture was cooled to room temperature, treated with water (100 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 100 ml). The extracts were washed with brine (50 ml), dried ($MgSO_4$), and evaporated in vacuo to give the product as a yellow oil (1.29 g) which was used in the next Example without further purification.

Example 11

N-(2-(1-(4-(4-Fluoro-2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

A stirred solution of the product of Example 10 (1.26g, 3.8 mmol) in dichloromethane (20 ml) under Ar was treated with di-isopropylethylamine (1.4 ml, 8.4 mmol) and cyclohexanecarbonyl chloride (1 ml, 7.5 mmol), washed after 24 hr with water (20 ml), saturated aq. $NaHCO_3$, (20 ml), and water (20 ml), dried ($MgSO_4$) and evaporated in vacuo to give a yellow oil which was purified by chromatography (silica; ethyl acetate). A solution of the oil in methanol (5 ml) was acidified with ethereal hydrogen chloride and evaporated in vacuo to give the trihydrochloride salt of the product (10.5g, 30%), m.p. 160-172 • C.
(Found: C, 54.7; H, 6.4; N, 10.1% $C_{25}H_{33}FN_4O_2$.3HCl requires C, 54.6; H, 6.6; N 10.2%).

Example 12

5-Nitro-2,3-dihydro-1,4-benzodioxin

1,2-Dibromoethane (12.0 g, 0.064 mol), potassium carbonate (17.6 g, 0.127 mol) and tetra-n-butyl ammonium bromide (1.37 g, 0.0043 mol) were added to a stirred solution of 3-nitrocatechol (6.59 g, 0.043 mol) in toluene (210 ml). The solution was heated at reflux with azeotropic removal of water for 23 h, cooled to room temperature, washed with 2N sodium hydroxide solution (150 ml), dried (Na_2SO_4), and evaporated in vacuo to give an orange oil. Purification by column chromatography (silica; ether) gave the product (2.55 g), m.p. 55-59 • C.

Example 13

2,3-Dihydro-1,4-benzodioxin-5-amine

Ammonium formate (3.40 g, 0.054 mol) and 10% palladium on charcoal (1.44 g) were added to a stirred solution of the product of example 12 (2.45 g, 0.0135 mol) in methanol (15 ml). After the considerable effervescence had ceased, the mixture was filtered, evaporated in vacuo and triturated with acetonitrile. The residue was purified by chromatography (silica; ether) to give the product (1.51 g).

Example 14

1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazine

The solution of the product of example 13 (1.50 g, 0.010 mol) and bis(2-chloroethyl)amine hydrochloride (1.77 g 0.01 mol) in chlorobenzene (20 ml) was heated under reflux for 24 h, cooled to room temperature and evaporated in vacuo. The white solid was dissolved in aqueous sodium hydroxide (100 ml) and extracted into ethyl acetate (3 x 50 ml). The extracts were dried ($MgSO_4$) and evaporated in vacuo to give the product (2.00 g).

Example 15

2-(1-(4-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazinyl))-N-(pyridin-2-yl)acetamide

A stirred solution of 2-chloro-N-(2-pyridinyl)acetamide (9.9 g, 58 mmol) in dry DMF (40 ml) at 0 °C was treated with the product of example 14 (58 mmol) in dry DMF (40 ml), treated with potassium carbonate (9.2 g, 67 mmol), after 30 min warmed to room temperature and after 18 h treated with water (400 ml). The emulsion was extracted with ether (3 x 200 ml) and the extracts washed with water (500 ml), dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. Purification by chromatography (silica; ethyl acetate) gave the product as an oil.

Example 16

1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-(2-pyridinylamino)ethyl)piperazine

A solution of the product of Example 15 (42.5 mmol) in THF (150 ml) was heated under reflux under Ar, treated dropwise with borane-dimethyl sulphide (8 ml, 84.3 mmol), after 2½ h treated dropwise with methanol (50 ml) and treated with ½N-HCl (200 ml). After 1 h the reaction mixture was cooled to room temperature, washed with ethyl acetate (2 x 200 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were dried (Na_2SO_4) and evaporated in vacuo. Purification by chromatography, [silica; ethyl acetate - ethanol (20:1)] gave the product as an oil.

Example 17

N-(2-(1-(4-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

A stirred suspension of potassium hydride, 35 wt.% suspension in mineral oil (2.99 g, ca. 26.1 mmol) in DMF (25 ml) was treated dropwise under Ar with the product of Example 16 (6.9 mmol) in DMF (15 ml). The reaction mixture was treated dropwise after 20 min with cyclohexanecarbonyl chloride (1.4 ml, 10.5 mmol), and after 1 h treated carefully with water (200 ml), acidified with 2N-HCl (ca. 70 ml), washed with hexane (2 x 200 ml), basified with 2N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were washed with brine (100 ml), dried (Na_2SO_4), and evaporated in vacuo to give a red oil which was purified by chromatography (silica; ethyl acetate). A solution of the oil in methanol (40 ml) was acidified with ethereal hydrogen chloride and evaporated in vacuo to give the hydrochloride salt of the product (1.04 g), m.p. 125-131 °C.

(Found: C, 62.6; H, 7.3; N, 11.0 $C_{26}H_{34}N_4O_2.HCl.¾H_2O$ requires C, 62.4; H, 7.35; N 11.2%)

Example 18

2-(1-(4-(3-(1,2-Benzisothiazolyl))piperazinyl))-N-(2-pyridinyl)acetamide

A solution of 3-piperazino-1,2-benzisothiazole (2.06 g, 6.4 mmol) in DMF (10 ml) was treated with N,N-diisopropylethylamine (2 ml, 12.3 mmol), treated with N-(2-pyridinyl)chloroacetamide (1.84 g, 9.6 mmol) in DMF (10 ml), stirred for 63 h, treated with water (150 ml), and extracted with ethyl acetate (3 x 50 ml). The extracts were evaporated in vacuo and the residue purified by chromatography (silica; ethyl acetate) to give the product as a foam (2.63 g).

Example 19

2-[1-[4-[3-(1,2-Benzisothiazolyl)]]piperazinyl]-N-(2-pyridyl)ethylamine

Borane-methyl sulphide complex (10M; 4.0ml, 40 mmol) was added dropwise to a stirred solution of the product of Example 18 (2.63 g, 7.44 mmol) in THF (26ml) under Ar. After 18 h, the solution was cooled to 0 °C, treated with methanol (10 ml), water (10 ml) and concentrated aq. HCl (10 ml), heated to reflux, cooled to room temperature and evaporated in vacuo. The yellow solid residue was treated with water (50 ml) and 12.5 N NaOH (16 ml). The mixture was extracted with CH_2Cl_2 (2 x 50 ml) and the extracts dried (Na_2SO_4), evaporated in vacuo and the gum chromatographed (Al_2O_3; ethyl acetate) to give the product as a clear pink oil (0.986 g).

Example 20

N-[2-[1-[4-[3-(1,2-Benzisothiazolyl)]]piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide

A solution of cyclohexanecarbonyl chloride (0.40 ml, 3.0 mmol) in CH_2 Cl_2 (25 ml) was added dropwise to a stirred solution of the product of Example 19 (0.99 g, 2.90 mmol) and C_5H_5N (0.32 ml, 4.0 mmol) in CH_2 Cl_2(10 ml) at 0 °C under Ar. The orange solution was stirred at room temperature for 18 h, washed with water (25 ml) and saturated aq. NaHCO (10 ml), dried (Na_2SO_4) and evaporated in vacuo to give an orange oil which was chromatographed (SiO_2; ethyl acetate) to give the product (0.84 g). The hydrochloride salt was prepared in standard fashion and crystallised by trituration with acetonitrile to give colourless crystals (0.84 g) m.p. 174 °-176 °C.
Found: C, 56.92; H, 6.64; N 13.24% $C_{25}H_{31}N_5OS$. 2HCl.0.25$H_2$0 requires C, 56.97; H, 6.41; N, 13.29%.

Example 21

1-[4-Benzyl-(1-piperazinyl)]isoquinoline

A solution of 1-chloroisoquinoline (1.64 g 10 mmol) in dry DMF (5 ml) was added to a stirred solution of 1-benzylpiperazine (1.85 g, 10.5 mmol) and N,N-diisopropylethylamine (2 ml, 1.5 g, 11.5 mmol) in dry DMF (5 ml) under Ar at room temperature. The solution was stirred at room temperature for 17 h. The yellow solution was heated at 110 °C for 7 h, treated with water (100 ml) and extracted with ether (2 x 50 ml). The extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed ($Si0_2$; ethyl acetate) to give the product (1.233 g).

Example 22

1-[1-Piperazinyl]isoquinoline

Ammonium formate (1.01 g, 16.0 mmol) and 10% Pd/C 42.5 mg, 0.4 mmol, 10 mol%) were added successively to a stirred solution of the product of Example 21 (1.23 g, 4.06 mmol) in methanol (4 ml). The mixture was stirred at room temperature for 6 h and was heated at 75 °C for 16 h. Methanol (40 ml) was added and the mixture filtered through Kieselguhr, and concentrated in vacuo to give the product as a pale yellow oil.

Example 23

1-[1-(5,6,7,8-Tetrahydro)naphthyl]piperazine

Bis(2-chloro)ethylamine hydrochloride (8.70 g, 48.7 mmol) was added to a stirred solution of 5,6,7,8-tetrahydro-1-naphthylamine (4.78 g 3 .5 mmol) in chlorobenzene (90 ml). The mixture was heated at 140 • C for 38 h and cooled to room temperature. The precipitate was collected and washed with a minimum volume of chlorobenzene. Recrystallisation from ethanol gave the hydrochloride salt of the product as white crystals (2.4 g), m.p. 324 • C (decomp).
Found: C, 66.8; H, 8.5; N, 11.1. $C_{14}H_20N_2$.HClrequires: C, 66.5; H, 8.4; N 11.1%.

Example 24

(S)-(1-(2-(2-Pyridylamino)propyl))-4-(2-methoxyphenyl)piperazine

(S)-1-(2-Aminopropyl))-4-(2-methoxyphenyl)piperazine (25 g, 100 mmol) was stirred with 2-fluoropyridine (2.6 ml, 30 mmol) in a bomb at 130 • C for 10 days. The resulting dark residue was dissolved in 150 ml water and basified with sodium hydroxide solution. The mixture was shaken with three portions of chloroform and the chloroform solution washed with water and dried over magnesium sulphate. The residual black oil (20 g) was chromatographed (silica), eluting with ethyl acetate to yield the product (1.84 g) as an oil.

Example 25

(R)-(1-(2-(2-Pyridylamino)propyl))-4-(2-methoxyphenyl)piperazine

(R)-(1-(2-(2-Pyridylamino)propyl))-4-(2-methoxyphenyl)piperazine was prepared from (R)-(1-(2-aminopropyl))-4-(2-methoxyphenyl)piperazine (30.8 g, 123 mmol) and 2-fluoropyridine (3.0 ml, 27.4 mmol) by the method described for Example 24 as an oil (5 g).

Example 26

3-[4-(2-Methoxyphenyl)piperazin-1-yl]propionitrile

A solution of acrylonitrile (1.06 g, 20 mmol) in ethanol (50 ml) was added to a stirred solution of 2-methoxyphenylpiperazine (3.84 g, 20 mmol) in ethanol (100 ml). After 18 h, the solvent was evaporated in vacuo to give the product (4.5 g) as a white solid.

Example 27

4-(2-Methoxyphenyl)-1-(3-aminopropyl)piperazine

A solution of the product of Example 26 (4.4 g, 18 mmol) in concentrated ethanolic ammonia solution (150 ml) was hydrogenated over 5% rhodium on alumina powder (0.6 g) at 50 p.s.i. (about 3.4 x 10^5 Pa) for 50 h to give the product (3.9 g) as a brown oil.

Example 28

4-(2-Methoxyphenyl)-1-(3-(pyridin-2-yl)aminopropyl)piperazine

The product of Example 27 (3.9 g, 16 mmol) and 2-chloropyridine (1.82 g, 16 mmol) were heated at 160 • C in a sealed vessel for 6 h. After cooling, the residue was taken up into CH_2Cl_2 (50 ml) washed with aqueous NaOH (3 x 50 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by chromatography [alumina; ethyl acetate - toluene (1:4)] to give the product (0.7 g) as a brown oil.

Example 29

1-(2-(2-Quinolinylamino)ethyl)-4-(2-methoxyphenyl)piperazine

1-(2-aminoethyl)-4-(2-methoxyphenyl)piperazine (9.4 g, 40 mmol) and 2-chloroquinoline (6.5 g, 40 mmol) were heated at 160 °C for 3 h, then at 120 °C for 18 h in a sealed vessel. The resultant brown tar was taken up into dilute hydrochloric acid (300 ml), washed with dichloromethane (3 x 100 ml) basified with sodium hydroxide, extracted into dichloromethane (3 x 100 ml), dried ($MgSO_4$) then evaporated in vacuo to give a brown oil. The oil was purified by chromatography [alumina; ethyl acetate - toluene (1:4)] to give the product (1.8 g) as a clear oil.

Example 30

N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(1-piperidinylcarbonyl)-2-aminopyridine

A stirred solution of the product of Example 2 (1 g, 3.2 mmol) in toluene (50 ml) was treated with diisopropylethylamine (0.84 ml, 4.8 mmol), treated dropwise with phosgene, about 12½% w/w solution in toluene (7.5 ml, about 8.6 mmol) with water-bath cooling under an atmosphere of Ar, after 1 h treated with piperidine (1.5 ml, 15 mmol), after 18 h treated with water (100 ml) and extracted with ethyl acetate (2 x 100 ml). The extracts were washed with water (100 ml), dried ($MgSO_4$), and evaporated in vacuo. The oil was purified by chromatography [silica, ethyl acetate - ethanol (20:1)], dissolved in ethanol (10 ml) and acidified with ethereal hydrogen chloride. Evaporation in vacuo gave the product as a pink glass (0.43 g), m.p. softens above 70 °C.
Found: C, 50.2; H, 7.4; N, 10.7. $C_{24}H_{33}N_5O_2.3HCl.\ 2\frac{1}{2}H_2O.1\frac{1}{2}$ EtOH requires C, 50.1; H, 7.8; N, 10.8%

Example 31

N-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-N-(pyridin-2-yl)-N'-cyclohexylthiourea

A suspension of the product of Example 2 (3.12 g, 10 mmol) in DMSO (50 ml) was added to KH, 35 wt. % dispersion in mineral oil (1 g, 8.7 mmol) under Ar. After 1 h, cyclohexylisothiocyanate (1.41 g, 10 mmol) was added and the mixture was stirred at 80 °C for 16 h, cooled to room temperature, and poured onto 2N-HCl (500 ml). The mixture was washed with ethyl acetate (3 x 200 ml), basified with NaOH, and extracted with ethyl acetate (3 x 100 ml). The extracts were dried ($MgSO_4$) and evaporated in vacuo to give an oil which was purified by chromatography [alumina; ethyl acetate-hexane (1:4)]and radial chromatography [silica; chloroform-ethanol (100:1)] to give the product (0.1 g) as an oil.
(Found: C, 66.3; H, 7.8: N, 15.4. $C_{25}H_{35}N_5OS$ requires C, 66.2; H, 7.8; N, 15.4%).

Example 32

2-(1-(4-(2-Hydroxyphenyl)piperazinyl))-N-(2-pyridinyl)ethylamine

The product of Example 2 (5.25 g, 16.8 mmol) in DMF (40 ml) was treated with potassium tert-butoxide (4.53 g, 40 mmol) under Ar, treated with propanethiol (3.14 g, 41.3 mmol), stirred at 100 °C for 18 h, cooled to room temperature, and poured onto water (200 ml). The mixture was extracted with ethyl acetate (3 x 80 ml) and the organic phases combined, washed with water (40 ml), dried ($MgSO_4$) and evaporated in vacuo. Purification by chromatography [alumina; hexane-ethyl acetate (1:1)] gave the product as an oil (2.79 g). The trihydrochloride salt was a colourless solid, m.p. 260-265 °C.

Example 33

N-(2-(4-(2-Hydroxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

A solution of the product of Example 32 (0.87 g, 2.9 mmol) in dichloromethane (10 ml) was treated with pyridine (0.46 g, 5.8 mmol) and cyclohexanecarbonyl chloride (0.85 g, 5.8 mmol). Th mixture was stirred for 18 h, evaporated in vacuo, treated with 10% NaOH (10 ml) and ethanol (10 ml), stirred for 2 h, acidified with dil. HCl (which cleaved the phenol ester), basified with saturated aq. $NaHCO_3$, and extracted with dichloromethane (3 x 30 ml). The extracts were washed with water (30 ml), dried ($MgSO_4$), and evaporated

in vacuo. The oil was purified by chromatography (silica; ethyl acetate) to give the product (1.09 g) as an oil. The hydrochloride salt was formed in the usual manner as a colourless powder, m.p. 220-223 °C (Found: C, 61.5; H, 7.6; N, 11.4. $C_{24}H_{32}N_4O_2$. $1\frac{1}{2}HCl$ $\frac{1}{4}H_2O$ requires C, 61.6; H, 7.3: N, 12.0%

Examples 34-39

The following compounds were prepared by a procedure which was analogous to that described in Example 18.

(a) Example 34

N-(2-Pyridinyl)-2-(1-(4-(1-naphthyl)piperazinyl))-acetamide was prepared from 1-(1-naphthyl)piperazine hydrochloride (2.49 g, 10 mmol) and N-(2-pyridinyl)chloroacetamide (1.69 g, 9.9 mmol) as colourless crystals (3.01 g), m.p. 171-173 °C

(Found: C, 72.5; H, 6.35; N, 16.1. $C_{21}H_{22}N_4O$ requires C, 72.8; H, 6.4; N, 16.2%)

(b) Example 35

2-(1-(4-(2-Methylphenyl)piperazinyl))-N-(2-pyridinyl)acetamide was prepared from ortho-tolylpiperazine hydrochloride (3.19 g, 15 mmol) and N-(2-pyridinyl)-2-chloroacetamide (2.56 g, 15.0 mmol) as a yellow gum (4.63 g).

(c) Example 36

2-(1-(4-(1-Isoquinolinyl)piperazinyl))-N-(2-pyridyl)acetamide was prepared from the product of Example 22 (707 mg, 3.3 mmol) and N-(2-pyridyl)chloroacetamide (568 mg, 3.33 mmol) as a yellow oil (1.16 g)

(d) Example 37

2-(1-(4-(1-(7-Methoxy)naphthyl)piperazinyl))-N-(2-pyridyl)acetamide was prepared from 1-[1-(7-methoxy)]-naphthyl piperazine (3.33 g, 13.8 mmol) and N-(2-pyridyl)chloroacetamide (1.88 g, 11.0 mmol), as a solid (3.125 g) m.p. 142 °-144 °C

(Found: C, 68.6; H, 6.6; N 14.3 $C_{22}H_{24}N_4O_20.5H_2O$ requires: C, 68.55; H, 6.5; N, 14.5%)

(e) Example 38

2-(1-(4-(1-(2-Methoxy)naphthyl)piperazinyl))-N-(2-pyridyl)acetamide was prepared from 1-[1-(2-methoxy)-naphthyl]piperazine hydrochloride three quarters hydrate (1.75 g, 5.99 mmol) and N-(2-pyridyl)-chloroacetamide (1.08 g, 6.33 mmol) as a solid (1.71 g), m.p. 184-185 °C (from ether)

(Found: C, 69.9; H, 6.5; N, 14.8 $C_{22}H_{24}N_4O_2$ requires C, 70.2; H, 6.4; N, 14.9%)

(f) Example 39

2-(1-(4-(1-(5,6,7,8-Tetrahydro)naphthyl)piperazinyl))-N-(2-pyridyl)acetamide was prepared from the product of Example 23 (2.88 g, 9.96 mmol) and N-(2-pyridyl)chloroacetamide as a colourless gum (2.50 g)

Examples 40-45

The following compounds were prepared by a procedure which was analogous to that described for Example 19.

(a) Example 40

2-(1-(4-(1-Napthyl))piperazinyl)-N-(2-pyridinyl)ethylamine was prepared from the product of Example 34 (2.965 g, 8.6 mmol) and borane-methyl sulphide complex (10 M; 4.0 ml, 40 mmol) as an oil (2.33 g)

(b) Example 41

2-(1-(4-(2-Methylphenyl))piperazinyl)-N-(2-pyridinyl)ethylamine was prepared from the product of Example 35 (4.63 g, 14.9 mmol) as a colourless oil (3.235 g).

(c) Example 42

2-[1-[4-(1-Isoquinolinyl)piperazinyl]]-N-(2-pyridyl)ethylamine was prepared from the product of Example 36 (975 mg, 2.8 mmol) and borane-methyl sulphide complex (10 M; 1.4 ml, 14 mmol) as an oil (0.695 g)

(d) Example 43

2-[1-[4-[1-(7-Methoxy)naphthyl]]piperazinyl]-N-(2-pyridyl)ethylamine was prepared from the product of Example 37 (3.0 g, 8.0 mmol) and borane-methyl sulphide complex (10 M; 4.0 ml, 40 mmol) as an oil (2.57 g).

(e) Example 44

2-[1-[4-[1-(2-Methoxy)naphthyl]]piperazinyl]-N-(2-pyridyl)ethylamine was prepared from the product of Example 38 (1.665 g, 4.4 mmol) and borane-methyl sulphide complex (2.4 ml, 24 mmol) as a yellow oil (1.229 g).

(f) Example 45

2-[1-[4-[1-(5,6,7,8-Tetrahydro)naphthyl]]piperazinyl]-N-(2-pyridyl)ethylamin was prepared from the product of Example 39 (2.50 g, 7.1 mmol) and borane-methyl sulphide complex (10 M; 3.8 ml, 38 mmol) as a

colourless gum (1.96 g).

Examples 46-65

The following compounds were prepared by a procedure analogous to that described for Example 20

(a) Example 46
N-(2-(1-(4-(1-Naphthyl))piperazinyl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide was prepared from the product of Example 40 (2.33 g, 7.0 mmol) and cyclohexanecarbonyl chloride (0.94 ml, 7.0 mmol). The dihydrochloride salt was produced as a colourless solid (2.56 g), m.p. 188-190 • C
(Found: C, 65.3; H, 7.1; N, 10.8. $C_{28}H_{34}N_4O.2HCl$ requires C, 65.2; H, 7.0; N, 10.9%).

(b) Example 47
N-(2-(1-(4-(2-Methylphenyl))piperazinyl)ethyl)-N-(2- pyridinyl)cyclohexanecarboxamide was prepared from the product of Example 41 (3.235 g, 10.9 mmol) as a dihydrochloride salt (3.66 g), m.p. 191-199 • C
(Found: C, 60.3; H, 7.65; N, 11.3 $C_{25}H_{34}N_4O$ $2HCl.H_2O$ requires C, 60.4; H, 7.7; N, 11.3%).

(c) Example 48
N-(2-(1-(4-(2-Fluorophenyl))piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide maleate hydrate was prepared as a white solid, m.p. 121-127 • C
(Found: C, 61.75; H, 6.7; N, 10.2 $C_{24}H_{31}FN_4O$ requires C, 61.75; H, 6.85; N, 10.3%)

(d) Example 49
N-[2-[1-[4-(1-Isoquinolinyl)]piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide was prepared from the product of Example 42 (695 mg, 2.1 mmol) and cyclohexanecarbonyl chloride (0.3 ml, 2.2 mmol). The trihydrochloride salt was a colourless solid (0.392 g) m.p. 145 • C.
(Found: C, 55.35; H, 7.01; N, 11.99 $C_{27}H_{33}N_5O$. $3HCl.2H_2O$ requires C, 55.06; H, 6.85; N, 11.89%)

(e) Example 50
N-[2-[1-[4-[1-(7-Methoxy)naphthyl]]piperazinyl]ethyl]-N -(2-pyridyl)cyclohexanecarboxamide was prepared from the product of Example 43 (2.57 g, 7.1 mmol) and cyclohexane carbonyl chloride (1.75 g, 12 mmol). The hydrochloride salt was a low melting solid (2.36 g) m.p. 90 • C (slowly decomposes above this temperature).
(Found: C, 66.17; H, 7.35; N, 10.38; $C_{29}H_{36}N_4O_2$ $HCl.H_2O$ requires C, 66.08; H, 7.46; N, 10.63%).

(f) Example 51
N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridyl)adamantane-1-carboxamide was prepared from the product of Example 2 and adamantane-1-carbonyl chloride. The dihydrochloride salt was a white solid, m.p. 132-136 • C
(Found: C, 58.6; H, 7.5; N, 9.2. $C_{29}H_{38}N_4O_2$. $2HCl.2\frac{1}{2}H_2O$ requires C, 58.8; H, 7.65; N, 9.45%).

(g) Example 52
N-[2-[1-[4-[1-(2-Methoxy)naphthyl]]piperazinyl]ethyl]-N-[2-pyridyl)cyclohexanecarboxamide was prepared from the product of Example 44 (1.23 g, 3.4 mmol) and cyclohexanecarbonyl chloride (0.7 ml, 0.8 g, 5.2 mmol). The dihydrochloride salt was obtained as colourless crystals (0.83 g), m.p. 151-156 • C
(Found: C, 63.6; H, 7.1; N, 10.6. $C_{29}H_{36}N_4O_2$. $2HCl$ requires C, 63.85; H, 7.0; N, 10.3%).

(h) Example 53
N-[2-[1-[4-[1-(5,6,7,8-Tetrahydro)naphthyl]]-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide was prepared from the product of Example 45 (1.96 g, 5.8 mmol) and cyclohexanecarbonyl chloride (1 ml, 1.1 g, 7.5 mmol). The dihydrochloride salt was obtained (2.21 g), m.p. 178-180 • C
(Found: C, 64.6; H, 7.8; N, 10.9. $C_{28}H_{38}N_4O.2HCl$ requires C, 64.7; H, 7.8; N, 10.8%)

(i) Example 54
(S)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane carboxamide was prepared from the product of Example 24 (1.84 g, 5.6 mmol) and cyclohexanecarbonyl chloride (0.8 ml, 5.6 mmol). The trihydrochloride salt was prepared as crystals (1.29 g) m.p. 178-180 • C, $[\alpha]_D^{26}$ = +61 • (methanol)
(Found: C, 57.7; H, 7.5; N , 10.32. $C_{26}H_{36}N_4O_2$. $3HCl$ requires C, 57.2; H, 7.2; N, 10.26%)

(j) Example 55
(R)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane carboxamide was prepared from the product of Example 25 (1.87 g, 5.7 mmol) and cyclohexanecarbonyl chloride (0.8 ml, 5.6 mmol). The dihydrochloride salt was prepared as crystals (2.1 g), m.p. 175-180 • C, $[\alpha]_D^{26}$ = -60 • (methanol)
(Found: C, 59.8; H, 7.8; N, 10.45. $C_{26}H_{36}N_4O_2$. $2HCl.\frac{3}{4}H_2O$ requires C, 59.7; H, 7.6; N, 10.7%).

(k) Example 56
N-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl]-N-(2-pyridinyl)cyclohexanecarboxamide was prepared

from the product of Example 28 (0.7 g, 2.1 mmol) and cyclohexanecarbonyl chloride (0.63 g, 4.3 mmol). The trihydrochloride salt was a white solid (0.9 g), m.p. 137-141 °C
(Found: C, 55.6; H, 7.3; N, 9.8. $C_{26}H_{36}N_4O_2$. 3HCl.H_2O requires C, 55.4; H, 7.3; N, 9.9%).

(l) Example 57

N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-quinolinyl)cyclohexane carboxamide was prepared from the product of Example 29 (1.8 g, 5 mmol) and cyclohexanecarbonyl chloride (1.42 ml, 10 mmol). The monohydrochloride salt was a white solid (2.31 g), m.p. 189-192 °C
(Found: C, 66.7; H, 7.3; N, 10.5; $C_{29}H_{36}N_4O_2$. HCl. $\frac{3}{4}H_2O$ requires C, 66.6; H, 7.4; N, 10.7%).

(m) Example 58

(Rac)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)cyclohexanecarboxamide was prepared from (rac)-4-(2-methoxyphenyl)-1-(2-(1-(2-pyridylamino)propyl))piperazine (2.28 g, 7 mmol) and cyclohexanecarbonyl chloride (1.03 ml, 7.7 mmol). The dihydrochloride salt (0.68 g) was obtained, m.p. 195-196 °C (from ethanol-ether)
(Found: C, 60.7; H, 7.2; N, 10.9. $C_{26}H_{36}N_4O_2$. 2HCl. $\frac{1}{4}H_2O$ requires C, 60.75; H, 7.55; N, 10.9%).

(n) Example 59

(S)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)cyclohexanecarboxamide was prepared from (S)-4-(2-methoxyphenyl)-1-(2-(1-(2-pyridylamino)propyl))piperazine [itself prepared from (R)-2-chloropropionyl chloride] by a method analogous to that used for Example 58. The trihydrochloride salt was a white solid, m.p. 129-130 °C, $[\alpha]_D^{25}$ = -25 ° (c = 1, methanol)
(Found: C, 54.7; H, 7.2; N, 9.5. $C_{26}H_{36}N_4O_2$. 3HCl. $1\frac{1}{4}H_2O$ requires C, 54.5; H, 7.4; N, 9.8%).

(o) Example 60

(R)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)propyl-N-(2-pyridyl)cyclohexanecarboxamide was prepared in a fashion similar to that used for Example 59.

(p) Example 61

N-(2-(4-Phenyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide was prepared from 2-(4-phenyl-1-piperazinyl)-N-(2-pyridyl)ethylamine and cyclohexanecarbonyl chloride. The trihydrochloride salt was a white solid, m.p. 198-200 °C
(Found: C, 57.2; H, 7.1; N, 11.1 $C_{24}H_{32}N_4O$. 3HCl requires C, 57.4; H, 7.0; N, 11.2%).

(q) Example 62

N-(2-(4-(2-Isopropylphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide was prepared from 2-(4-(2-isopropylphenyl)-1-piperazinyl)-N-(2-pyridyl)ethylamine and cyclohexanecarbonyl chloride. The hydrochloride salt was a colourless powder, m.p. 168-170 °C
(Found: C, 67.15; H, 8.2; N, 11.5 $C_{27}H_{38}N_4O$.HCl.$\frac{3}{4}H_2O$ requires C, 66.9; H, 8.4; N, 11.6%).

(r) Example 63

N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethyl)-N-(4-pyridinyl)cyclohexane carboxamide was prepared from 2-(4-(2-methoxyphenyl-1-piperazinyl))-N-(4-pyridyl)ethylamine (0.39 g, 1.2 mmol) and cyclohexanecarbonyl chloride (0.37 ml, 2.5 mmol). The trihydrochloride salt (0.15 g) was a colourless solid, m.p. 151-153 °C.
(Found: C, 55.7; H, 7.3; N, 10.2 $C_{25}H_{34}N_4O_2$.3HCl.$\frac{1}{2}H_2O$ requires C, 55.5; H, 7.1; N, 10.4).

(s) Example 64

N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethyl)-N-(3-pyridyl)cyclohexanecarboxamide was prepared from 2-(4-(2-methoxyphenyl)-1-piperazinyl)-N-(3-pyridyl)ethylamine and cyclohexanecarbonyl chloride. The dihydrochloride salt was a hygroscopic white solid, m.p. 138-140 °C
(Found: C, 56.8; H, 7.8; N, 10.5 $C_{25}H_{34}N_4O_2$.2HCl. $2H_2O$ requires C, 56.7; H, 7.2; N, 10.6%).

(t) Example 65

N-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-pyridinyl)cyclohex-1-enecarboxamide was prepared from the product of Example 2, (1.49 g, 5 mmol) and cyclohex-1-enecarbonyl chloride (1.08 g, 7.5 mmol) as a clear oil
(Found: C, 71.3: H, 7.9; N, 13.0. $C_{25}H_{32}N_4O_2$ requires C, 71.4; H, 7.7; N, 13.3%)

Example 66

N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane thiocarboxamide

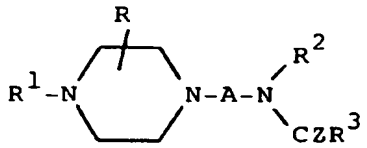
Phosphorous pentasulphide (2.0 g, 4.5 mmol) and sodium carbonate (0.47 g, 4.5 mmol) were added to THF (30 ml) and the resultant mixture was stirred vigorously with gentle warming until complete dissolution (30 min). The product of Example 3 (1.5 g, 3.55 mmol) in THF (10 ml) was added and the resultant mixture was stirred at room temperature for 16 h, boiled at reflux for 3 h and cooled to room temperature.

Lawesson's reagent (1.5 g, 3.71 mmol) and dioxane (30 ml) were add d and the mixture was boiled at reflux for 4 h. The cooled reaction mixture was washed into a solution of sodium hydroxide (10%, 100 ml) and dichloromethane (200 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 100 ml). The combined extracts were washed with brine (1 x 200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The resultant oil (1.0 g) was chromatographed on silica gel using dichloromethane and then 2% methanol in dichloromethane as eluents to afford an oil (280 mg). This oil was rechromatographed on alumina twice using dichloromethane as eluent to give an oil (50 mg). This was dissolved in ethanol and the dihydrochloride salt of the product was crystallised by the addition of ethereal HCl (50 mg), m.p. 108-110 °C
(Found: C, 58.5; H, 7.4; N, 10.85. $C_{25}H_{34}N_4OS$ 2HCl requires C, 58.7; H, 7.1; N, 10.95%).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, IT, LI, LU, NL, PT, SE

1. A compound of the general formula



(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein
A is an alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,
Z is oxygen or sulphur,
R is hydrogen or lower alkyl,
R^1 is a mono or bicyclic aryl or heteroaryl radical,
R^2 is a mono or bicyclic heteroaryl radical
and R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl(lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, COaryl, aryl(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom] or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl(lower)alkyl].

2. A compound as claimed in claim 1 in which A is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-CH(CH_3).CH_2-$.

3. A compound as claimed in claim 1 or 2 in which R is hydrogen.

4. A compound as claimed in any one of claims 1 to 3 in which R^1 is o-methoxyphenyl, o-isopropylphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dihydro[1,4]-benzodioxan-5-yl, pyrimid-2-yl, 1-naphthyl, 3-(1,2-benzisothiazolyl), 1-(7-methoxynaphthyl) or 1-(5,6,7,8-tetrahydro)naphthyl.

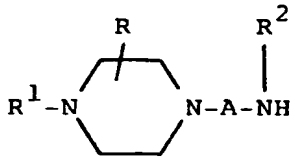
5. A compound as claimed in any one of claims 1 to 4 in which R^2 is pyridyl-2-yl, quinolin-2-yl or thiazol-2-yl.

6. A compound as claimed in any one of claims 1 to 5 in which R^3 is lower alkyl, cycloalkyl, cycloalkenyl, phenyl, piperidino or -NHcycloalkyl.

7. A compound as claimed in claim 1 which is N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-cyclohexyl-N'-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))ethyl)-N-(2-pyridinyl)urea or N-(2-(1-(4-(2-methoxyphenyl)piperaz inyl))ethyl)-N-(2-pyridinyl)benzamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)trimethylacetamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-thiazolyl)cyclohexanecarboxamide or N-(2-(1-(4-(4-fluoro-2-methox-

yphenyl)piperazinyl)) ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(1-(4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-[2-[1-[4-[3-(1,2-benzisothiazolyl)]]piperazinyl]-ethyl]-N-(2-pyridyl)cyclohexanecarboxamide or N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))ethyl)-N-(1-piperidinylcarbonyl)-2-aminopyridine or N-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(pyridin-2-yl)-N'-cyclohexylthiourea or N-(2-(4-(2-hydroxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(1-(4-(1-naphthyl))piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide or N-(2-(1-(4-(2-methylphenyl))piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexanecarboxamide or N-(2-(1-(4-(2-fluorophenyl))piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexanecarboxamide or N-[2-[1-[4-(1-isoquinolinyl)]piperazinyl]ethyl]-N-(2-pyridinyl)-cyclohexanecarboxamide or N-[2-[1-[4-[1-(7-methoxy)naphthyl]]piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridyl)adamantane-1-carboxamide or N-[2-[1-[4-[1-(2-methoxy)naphthyl]]piperazinyl]ethyl]-N-[2-pyridyl)cyclohexanecarboxamide or N-[2-[1-[4-[1-(5,6,7,8-tetrahydro)naphthyl]]piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide or (S)-N-(1-methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane carboxamide or (R)-N-(1-methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane carboxamide or N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-quinolinyl)cyclohexane carboxamide or (Rac)-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)cyclohexanecarboxamide or (S)-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)cyclohexanecarboxamide or (R)-N-(2-(4-(2-methoxyphenyl)-1-pi perazinyl)propyl-N-(2-pyridyl)cyclohexanecarboxamide or N-(2-(4-phenyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(4-(2-isopropylphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(4-pyridinyl)cyclohexane carboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(3-pyridyl)cyclohexanecarbo xamide or N-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-N-(2-pyridinyl)cyclohex-1-enecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane thiocarboxamide
or a pharmaceutically acceptable salt thereof.

8. A process for preparing a compound as claimed in claim 1 which comprises
(a) acylating an amine of formula (II)

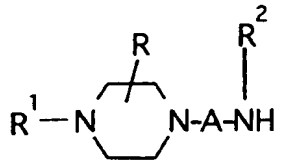


(II)

(where A, R, R^1 and R^2 have the meanings given in claim 1) with an acid of formula (III)

R^3CZOH (III)

(where Z and R^3 are as defined in claim 1) or with an acylating derivative thereof, or
(b) reacting an amine of formula (II)

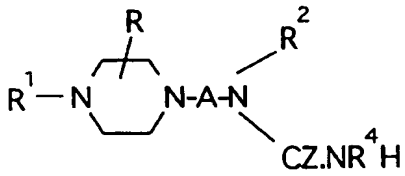


(II)

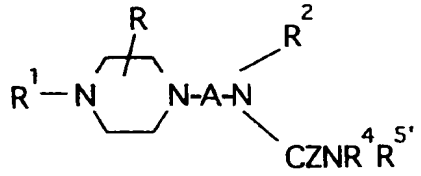
(where A, R, R^1 and R^2 are as d fined in claim 1) with an isocyanate or isothiocyanat of formula

R^5NCZ

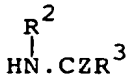
(where R^5 and Z are as defined in claim 1),
or
(c) acylating a compound of formula



(where R, R^1, R^2, R^4, A and Z are as defined in claim 1) to give a compound of formula

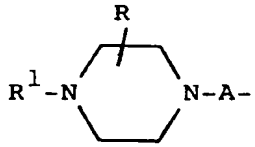


where R, R^1, R^2, R^4, A and Z are as defined in claim 1 and $R^{5'}$ is -CO(lower)alkyl or -COaryl,
or
(d) alkylating an amide or thioamide of formula (IV)



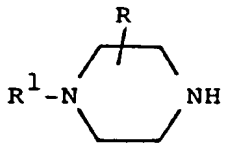
(IV)

(where R^2, R^3 and Z are as defined in claim 1) with an alkylating agent providing the group



(where R, R^1 and A are as defined in claim 1)
or

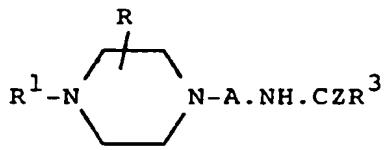
(e) alkylating a compound of formula



(where R and R^1 are as defined in claim 1) with a compound of formula

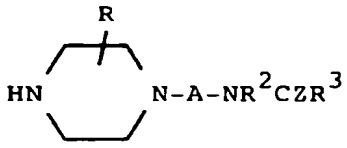
X-A $NR^2.CZ.R^3$ (V)

(where A, R, R^1, R^2, R^3 and Z are as defined in claim 1 and X is a leaving group)
or
(f) heteroarylating a compound of formula



(VI)

(where R, R^1, R^3, A and Z are as defined in claim 1) with a compound providing the heteroaryl group R^2 (where R^2 is as defined in claim 1) or
(g) reacting a piperazine compound of formula



(where R, R^2, R^3, A and Z are as defined in claim 1) with a fluoro compound of formula

R^1F

where R^1 is a mono or bicyclic aryl or heteroaryl radical that is activated towards nucleophilic substitution
or
(h) sulphurising a compound of formula (I) where Z is oxygen to give a compound of formula (I) where Z is sulphur
or
(i) converting a base claimed in claim 1 into a pharmaceutically acceptable acid addition salt thereof
or
(j) converting a pharmaceutically acceptable acid addition salt claimed in claim 1 into a free base.

9. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier.

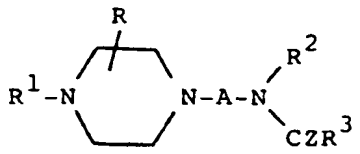
10. A compound as claimed in any one of claims 1 to 7 for use as a pharmaceutical.

11. A compound as claimed in any one of claims 1 to 7 for use as an anxiolytic, an antidepressant, a hypotensive or as an agent for regulating the sleep/wake cycle, feeding behaviour and/or sexual function.

12. 1-(2-Methoxyphenyl)-4-[2-(2-pyridinylamino)ethyl]piperazine

Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of the general formula



(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein

A is an alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,

Z is oxygen or sulphur,

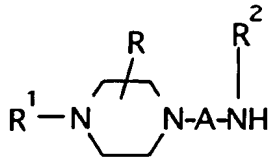
R is hydrogen or lower alkyl,

R^1 is a mono or bicyclic aryl or heteroaryl radical,

R^2 is a mono or bicyclic heteroaryl radical

and R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl(lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, COaryl, aryl(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom] or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl(lower)alkyl] which comprises

(a) acylating an amine of formula (II)



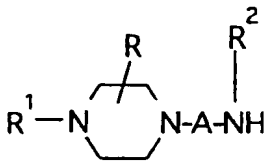
(II)

(where A, R, R^1 and R^2 have the meanings given above) with an acid of formula (III)

R^3CZOH (III)

(where Z and R^3 are as defined above) or with an acylating derivative thereof, or

(b) reacting an amine of formula (II)

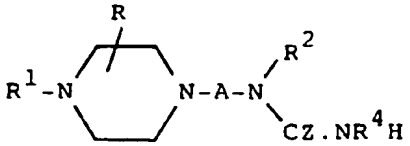


(II)

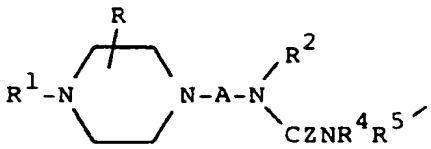
(where A, R, R^1 and R^2 are as defined above) with an isocyanate or isothiocyanate of formula

R^5NCZ

(where R^5 and Z are as defined above),
or
(c) acylating a compound of formula



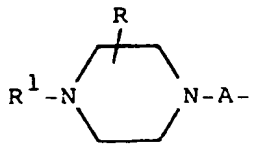
(where R, R^1, R^2, R^4, A and Z are as defined above) to give a compound of formula



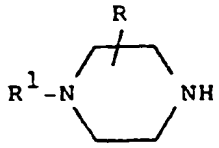
where R, R^1, R^2, R^4, A and Z are as defined above and $R^{5'}$ is -CO(lower)alkyl or -COaryl,
or
(d) alkylating an amide or thioamide of formula (IV)

(IV)

(where R^2 R^3 and Z are as defined above) with an alkylating agent providing the group



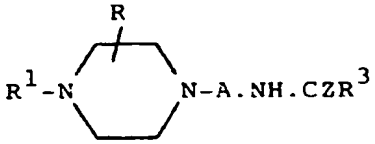
(where R, R^1 and A are as defined above)
or
(e) alkylating a compound of formula



(where R and R^1 are as defined above) with a compound of formula

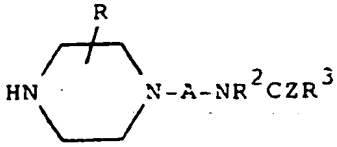
X-A . NR^2.CZ.R^3 (V)

(where A, R, R^1, R^2, R^3 and Z are as defined above and X is a leaving group)
or
(f) heteroarylating a compound of formula



(VI)

(where R, R^1, R^3, A and Z are as defined above) with a compound providing the heteroaryl group R^2 (where R^2 is as defined above) or
(g) reacting a piperazine compound of formula



(where R, R^2, R^3, A and Z are as defined above) with a fluoro compound of formula

R^1F

where R^1 is a mono or bicyclic aryl or heteroaryl radical that is activated towards nucleophilic substitution
or
(h) sulphurising a compound of formula (I) where Z is oxygen to giv a compound of formula (I) where Z is sulphur

or
(i) converting a base claimed of formula I into a pharmaceutically acceptable acid addition salt thereof
or
(j) converting a pharmaceutically acceptable acid addition salt of a compound of formula I into a free base thereof.

2. A process as claimed in claim 1 in which A is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-CH(CH_3).CH_2-$.

3. A process as claimed in claim 1 or 2 in which R is hydrogen.

4. A process as claimed in any one of claims 1 to 3 in which R^1 is o-methoxyphenyl, o-isopropylphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dihydro[1,4]benzodioxan-5-yl, pyrimid-2-yl, 1-naphthyl, 3-(1,2-benzisothiazolyl), 1-(7-methoxynaphthyl) or 1-(5,6,7,8-tetrahydro)naphthyl.

5. A process as claimed in any one of claims 1 to 4 in which R^2 is pyridyl-2-yl, quinolin-2-yl or thiazol-2-yl.

6. A process as claimed in any one of claims 1 to 5 in which R^3 is lower alkyl, cycloalkyl, cycloalkenyl, phenyl, piperidino or -NHcycloalkyl.

7. A process as claimed in claim 1 in which the product is N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-cyclohexyl-N'-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)urea or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)benzamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)trimethylacetamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-thiazolyl)cyclohexanecarboxamide or N-(2-(1-(4-(4-fluoro-2-methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(1-(4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-[2-[1-[4-[3-(1,2-benzisothiazolyl)]]piperazinyl]-ethyl]-N-(2-pyridyl)cyclohexanecarboxamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(1-piperidinylcarbonyl)-2-aminopyridine or N-(2-(4-(2-methoxyphenyl)-piperazin-1-yl)ethyl)-N-(pyridin-2-yl)-N'-cyclohexylthiourea or N-(2-(4-(2-hydroxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(1-(4-(1-naphthyl))piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide or N-(2-(1-(4-(2-methylphenyl))piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexanecarboxamide or N-(2-(1-(4-(2-fluorophenyl))piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexanecarboxamide or N-[2-[1-[4-(1-isoquinolinyl)]piperazinyl]ethyl]-N-(2-pyridinyl)-cyclohexanecarboxamide or N-[2-[1-[4-[1-(7-methoxy)naphthyl]]piperazinyl]ethyl]-N-(2-pyridyl)-cyclohexanecarboxamide or N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridyl)adamantane-1-carboxamide or N-[2-[1-[4-[1-(2-methoxy)naphth yl]]piperazinyl]ethyl]-N-[2-pyridyl)-cyclohexanecarboxamide or N-[2-[1-[4-[1-(5,6,7,8-tetrahydro)naphthyl]]piperazinyl]ethyl]-N-(2-pyridyl)-cyclohexanecarboxamide or (S)-N-(1-methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexane carboxamide or (R)-N-(1-methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane carboxamide or N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-N-(2-pyridinyl)-cyclohexanecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-quinolinyl)cyclohexane carboxamide or (Rac)-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)-cyclohexanecarboxamide or (S)-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)propyl)-N-(2-pyridyl)-cyclohexanecarboxamide or (R)-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)propyl-N-(2-pyridyl)-cyclohexanecarboxamide or N-(2-(4-phenyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or N-(2-(4-(2-isopropylphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(4-pyridinyl)cyclohexane carboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(3-pyridyl)cyclohexanecarboxamide or N-(2-(4-(2-methoxyphenyl)-piperazin-1-yl)ethyl)-N-(2-pyridinyl)cyclohex-1-enecarboxamide or N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexane thiocarboxamide
or a pharmaceutically acceptable salt thereof.

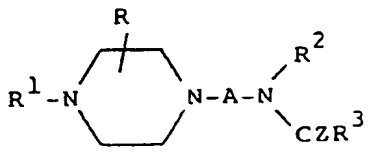
8. A process for preparing a pharmaceutical composition which comprises bringing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof into association with a pharmaceutically acc ptabl carrier.

9. A process as claimed in claim 1 wherein th active ingredient is prepared by the process claimed in any one of claims 1 to 7.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, IT, LI, LU, NL, PT, SE

1. Verbindung der allgemeinen Formel



(I)

oder ein pharmazeutisch annehmbares Säureadditionssalz hievon, worin A eine Alkylenkette mit 2 bis 4 Kohlenstoffatomen, gegebenenfalls substituiert durch eine oder mehrere nied.Alkylgruppen, bedeutet, Z Sauerstoff oder Schwefel darstellt, R Wasserstoff oder nied.Alkyl ist, R^1 einen mono- oder bicyclischen Aryl- oder Heteroarylrest bedeutet, R^2 einen mono- oder bicyclischen Heteroarylrest darstellt, und R^3 Wasserstoff, nied.Alkyl, Cycloalkyl, Cycloalkenyl, Cycloalkyl(nied.)alkyl, Aryl, Aryl(nied.)alkyl, Heteroaryl, Heteroaryl(nied.)alkyl, eine Gruppe der Formel $-NR^4R^5$ (wobei R^4 Wasserstoff, nied.Alkyl, Aryl oder Aryl(nied.)alkyl bedeutet, und R^5 Wasserstoff, nied.Alkyl, -CO-(nied.)Alkyl, Aryl, CO-Aryl, Aryl(nied.)-alkyl, Cycloalkyl oder Cycloalkyl(nied.)alkyl darstellt, oder R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie beide gebunden sind, einen gesättigten heterocyclischen Ring bilden, der ein weiteres Heteroatom enthalten kann) oder eine Gruppe der Formel OR^6 (wobei R^6 nied.Alkyl, Cycloalkyl, Cycloalkyl(nied.)alkyl, Aryl, Aryl(nied.)alkyl, Heteroaryl oder Heteroaryl(nied.)alkyl bedeutet) ist.

2. Verbindung nach Anspruch 1, worin A die Bedeutung $-(CH_2)_2-$,$-(CH_2)_3-$, $-(CH_2)_4-$ oder $-CH(CH_3).CH_2-$ hat.

3. Verbindung nach Anspruch 1 oder 2, worin R Wasserstoff ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, worin R^1 o-Methoxyphenyl, o-Isopropylphenyl, 4-Fluor-2-methoxyphenyl, 2,3-Dihydro[1,4]benzodioxan-5-yl, Pyrimid-2-yl, 1-Naphthyl, 3-(1,2-Benzisothiazolyl), 1-(7-Methoxynaphthyl) oder 1-(5,6,7,8-Tetrahydro)-naphthyl bedeutet.

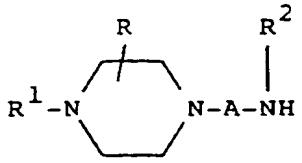
5. Verbindung nach einem der Ansprüche 1 bis 4, worin R^2 Pyridyl-2-yl, Chinolin-2-yl oder Thiazol-2-yl darstellt.

6. Verbindung nach einem der Ansprüche I bis 5, worin R^3 nied.Alkyl, Cycloalkyl, Cycloalkenyl, Phenyl, Piperidino oder -NH-Cycloalkyl ist.

7. Verbindung nach Anspruch 1, welche N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-Cyclohexyl-N'-(2-(1-(4-(2-methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridinyl)-harnstoff oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-benzamid oder N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridinyl)-trimethylacetamid oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-thiazolyl)-cyclohexancarboxamid oder N-(2-(1-(4-(4-Fluor-2-methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)cyclohexancarboxamid oder N-(2-(1-(4-(2,3-Dihydro-1,4-benzodioxin-5-yl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[2-[1-[4-[3-(1,2-Benzisothiazolyl)]]piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(1-piperidinylcarbonyl)-2-aminopyridin oder N-(2-(4-(2-Methoxyphenyl)-piperazin-1-yl)-ethyl)-N-(pyridin-2-yl)-N'-cyclohexylthioharnstoff oder N-(2-(4-(2-Hydroxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(1-(4-(1-Naphthyl))-piperazinyl)-ethyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methylphenyl))piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Fluorph nyl))-piperazinyl)-ethyl)-N-(2-pyridinyl)cyclohexancarboxamid oder N-[2-[1-[4-(1-Isochinolinyl)]piperazinyl]-ethyl]-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[2-[1-

[4-[1-(7-Methoxy)-naphthyl]]-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridyl)-adamantan-1-carboxamid oder N-[2-[1-[4-[1-(2-Methoxy)-naphthyl]]-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-[2-[1-[4-[1-(5,6,7,8-Tetrahydro)-naphthyl]]-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder (S)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder (R)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl]-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-chinolinyl)-cyclohexancarboxamid oder (rac)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder (S)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder (R)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(4-Phenyl-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Isopropylphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(4-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(3-pyridyl)cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-piperazin-1-yl)-ethyl)-N-(2-pyridinyl)-cyclohex-1-encarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)cyclohexanthiocarboxamid oder ein pharmazeutisch annehmbares Salz hievon ist.

8. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches umfaßt:
(a) Acylieren eines Amins der Formel (II)

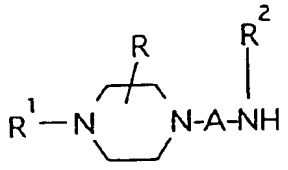


(II)

(worin A, R, R^1 und R^2 die in Anspruch 1 angegebenen Bedeutungen haben) mit einer Säure der Formel (III)

R^3CZOH (III)

(worin Z und R^3 wie in Anspruch 1 definiert sind) oder mit einem Acylierungsderivat hievon, oder
(b) Umsetzen eines Amins der Formel (II)



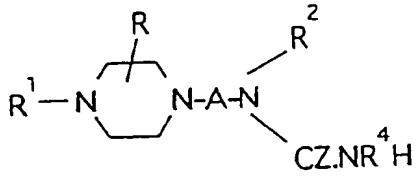
(II)

(worin A, R, R^1 und R^2 wie in Anspruch 1 definiert sind) mit einem Isocyanat oder Isothiocyanat der Formel

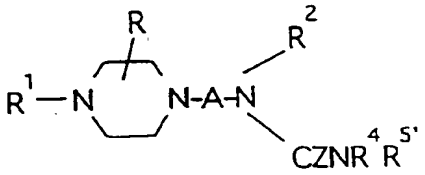
R^5NCZ

(worin R^5 und Z wie in Anspruch 1 definiert sind), oder

(c) Acylieren einer Verbindung d r Formel

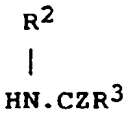


(worin R, R^1, R^2, R^4, A und Z wie in Anspruch 1 definiert sind), wobei eine Verbindung der Formel



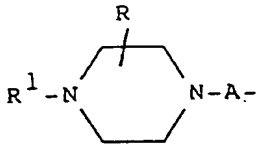
worin R, R^1, R^2, R^4, A und Z wie in Anspruch 1 definiert sind, und $R^{5'}$ die Bedeutung -CO-(nied.)-Alkyl oder -CO-Aryl hat, erhalten wird, oder

(d) Alkylieren eines Amids oder Thioamids der Formel (IV)



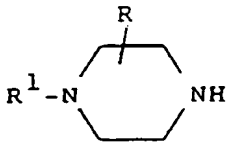
(IV)

(worin R^2, R^3 und Z wie in Anspruch 1 definiert sind) mit einem Alkylierungsmittel, welches die Gruppe



(worin R, R^1 und A wie in Anspruch 1 definiert sind) vorsieht, oder

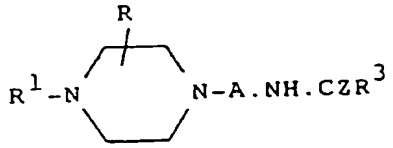
(e) Alkylieren einer Verbindung der Formel



(worin R und R^1 wie in Anspruch 1 definiert sind) mit einer Verbindung der Formel

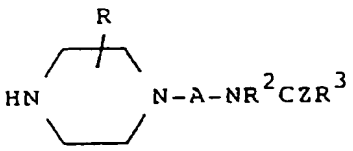
X-A.NR^2.CZ.R^3 (V)

(worin A, R, R^1, R^2, R^3 und Z wie in Anspruch 1 definiert sind, und X ine Abgangsgruppe darstellt), oder
(f) Heteroarylieren einer Verbindung der Formel



(VI)

(worin R, R^1, R^3, A und Z wie in Anspruch 1 definiert sind) mit einer Verbindung, die die Heteroarylgruppe R^2 (wobei R^2 wie in Anspruch 1 definiert ist) vorsieht, oder
(g) Umsetzen einer Piperazinverbindung der Formel



(worin R, R^2, R^3, A und Z wie in Anspruch 1 definiert sind) mit einer Fluorverbindung der Formel

R^1F ,

worin R^1 einen mono- oder bicyclischen Aryl- oder Heteroarylrest, der für nucleophile Substitution aktiviert ist, bedeutet, oder
(h) Schwefeln einer Verbindung der Formel (I), worin Z Sauerstoff darstellt, wobei eine Verbindung der Formel (I), worin Z Schwefel ist, erhalten wird, oder
(i) Überführen einer Base nach Anspruch 1 in ein pharmazeutisch annehmbares Säureadditionssalz hievon, oder
(j) Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes nach Anspruch 1 in eine freie Base.

9. Pharmazeutische Zusammensetzung, welche eine Verbindung nach einem der Ansprüche 1 bis 7 in Vereinigung mit einem pharmazeutisch annehmbaren Träger umfaßt.

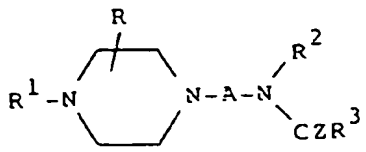
10. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung als Pharmazeutikum.

11. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung als Anxiolytikum, Antidepressivum, blutdrucksenkendes Mittel oder als Mittel zur Regulierung des Schlaf-Wach-Zyklus, des Eßverhaltens und/oder der Sexualfunktionen.

12. 1-(2-Methoxyphenyl)-4-[2-(2-pyridinylamino)-ethyl]piperazin.

Patentansprüche für folg nde Vertragsstaaten : ES, GR

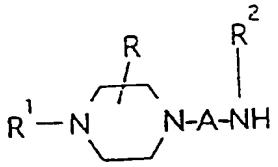
1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



(I)

oder eines pharmazeutisch annehmbaren Säureadditionssalzes hievon, worin A eine Alkylenkette mit 2 bis 4 Kohlenstoffatomen, gegebenenfalls substituiert durch eine oder mehrere nied.Alkylgruppen, bedeutet, Z Sauerstoff oder Schwefel darstellt, R Wasserstoff oder nied.Alkyl ist, R^1 einen mono- oder bicyclischen Aryl- oder Heteroarylrest bedeutet, R^2 einen mono- oder bicyclischen Heteroarylrest darstellt, und R^3 Wasserstoff, nied.Alkyl, Cycloalkyl, Cycloalkenyl, Cycloalkyl(nied.)alkyl, Aryl, Aryl-(nied.)alkyl, Heteroaryl, Heteroaryl(nied.)alkyl, eine Gruppe der Formel $-NR^4R^5$ (wobei R^4 Wasserstoff, nied.Alkyl, Aryl oder Aryl(nied.)alkyl bedeutet, und R^5 Wasserstoff, nied.Alkyl, -CO-(nied.)Alkyl, Aryl, CO-Aryl, Aryl(nied.)alkyl, Cycloalkyl oder Cycloalkyl(nied.)alkyl darstellt, oder R^4 und R^5 zusammen mit dem Stickstoffatom, an das sie beide gebunden sind, einen gesättigten heterocyclischen Ring bilden, der ein weiteres Heteroatom enthalten kann) oder eine Gruppe der Formel OR^6 (wobei R^6 nied.Alkyl, Cycloalkyl, Cycloalkyl(nied.)alkyl, Aryl, Aryl(nied.)alkyl, Heteroaryl oder Heteroaryl(nied.)alkyl bedeutet) ist, welches Verfahren umfaßt:

(a) Acylieren eines Amins der Formel (II)



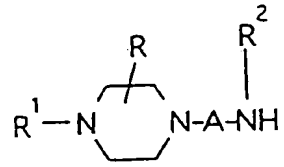
(II)

(worin A, R, R^1 und R^2 die oben angegebenen Bedeutungen haben) mit einer Säure der Formel (III)

R^3CZOH (III)

(worin Z und R^3 wie oben definiert sind) oder mit einem Acylierungsderivat hievon, oder

(b) Umsetzen eines Amins der Formel (II)



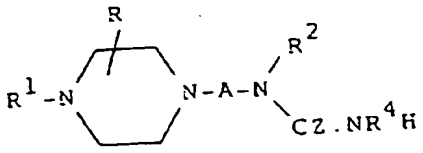
(II)

(worin A, R, R^1 und R^2 wie oben definiert sind) mit einem Isocyanat oder Isothiocyanat der Formel

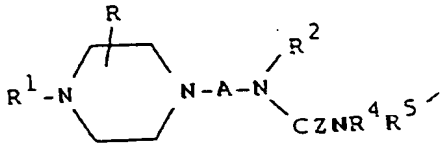
R^5NCZ

(worin R^5 und Z wie oben defini rt sind), oder

(c) Acylieren einer Verbindung der Formel



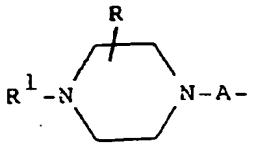
(worin R, R^1, R^2, R^4, A und Z wie oben definiert sind), wobei eine Verbindung der Formel



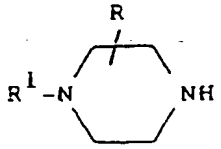
worin R, R^1, R^2, R^4, A und Z wie oben definiert sind, und $R^{5'}$ die Bedeutung -CO-(nied.)Alkyl oder -CO-Aryl hat, erhalten wird, oder
(d) Alkylieren eines Amids oder Thioamids der Formel (IV)

(IV)

(worin R^2, R^3 und Z wie oben definiert sind) mit einem Alkylierungsmittel, welches die Gruppe



(worin R, R^1 und A wie oben definiert sind) vorsieht, oder
(e) Alkylieren einer Verbindung der Formel

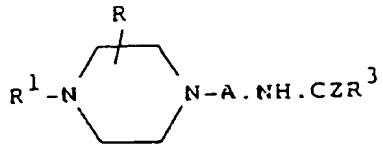


(worin R und R^1 wie oben definiert sind) mit einer Verbindung der Formel

X-A.NR^2.CZ.R^3 (V)

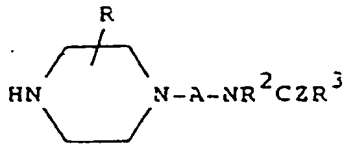
(worin A, R, R^1, R^2, R^3 und Z wie oben definiert sind, und X eine Abgangsgruppe darstellt), oder

(f) Heteroarylieren einer Verbindung der Formel



(VI)

(worin R, R^1, R^3, A und Z wie oben definiert sind) mit einer Verbindung, die die Heteroarylgruppe R^2 (wobei R^2 wie oben definiert ist) vorsieht, oder
(g) Umsetzen einer Piperazinverbindung der Formel



(worin R, R^2, R^3, A und Z wie oben definiert sind) mit einer Fluorverbindung der Formel

R^1F ,

worin R^1 einen mono- oder bicyclischen Aryl- oder Heteroarylrest, der für nucleophile Substitution aktiviert ist, bedeutet, oder
(h) Schwefeln einer Verbindung der Formel (I), worin Z Sauerstoff darstellt, wobei eine Verbindung der Formel (I), worin Z Schwefel ist, erhalten wird, oder
(i) Überführen einer Base der Formel (I) in ein pharmazeutisch annehmbares Säureadditionssalz hievon, oder
(j) Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes einer Verbindung der Formel (I) in eine freie Base hievon.

2. Verfahren nach Anspruch 1, wobei A die Bedeutung $-(CH_2)_2-$,$-(CH_2)_3-$, $-(CH_2)_4-$ oder $-CH(CH_3).CH_2-$ hat.

3. Verfahren nach Anspruch 1 oder 2, wobei R Wasserstoff ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei R^1 o-Methoxyphenyl, o-Isopropylphenyl, 4-Fluor-2-methoxyphenyl, 2,3-Dihydro[1,4]benzodioxan-5-yl, Pyrimid-2-yl, 1-Naphthyl, 3-(1,2-Benzisothiazolyl), 1-(7-Methoxynaphthyl) oder 1-(5,6,7,8-Tetrahydro)-naphthyl bedeutet.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei R^2 Pyridyl-2-yl, Chinolin-2-yl oder Thiazol-2-yl darstellt.

6. Verfahren nach einem der Ansprüche 1 bis 5, wobei R^3 nied.Alkyl, Cycloalkyl, Cycloalkenyl, Phenyl, Piperidino oder -NH-Cycloalkyl ist.

7. Verfahren nach Anspruch 1, bei welchem das Produkt N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-Cyclohexyl-N'-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-harnstoff oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-benzamid oder N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridinyl)-trimethylacetamid oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-thiazolyl)-cyclohexancarboxamid oder N-(2-(1-(4-(4-Fluor-2-methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2,3-Dihydro-1,4-benzodioxin-5-yl)-piperazinyl))-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[2-

[1-[4-[3-(1,2-Benzisothiazolyl)]]-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(1-piperidinylcarbonyl)-2-aminopyridin oder N-(2-(4-(2-Methoxyphenyl)-piperazin-1-yl)-ethyl)-N-(pyridin-2-yl)-N'-cyclohexylthioharnstoff oder N-(2-(4-(2-Hydroxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)cyclohexancarboxamid oder N-(2-(1-(4-(1-Naphthyl))-piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methylphenyl))-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Fluorphenyl))-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[2-[1-[4-(1-Isochinolinyl)]-piperazinyl]-ethyl]-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[2-[1-[4-[1-(7-Methoxy)-naphthyl]]piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(1-(4-(2-Methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridyl)adamantan-1-carboxamid oder N-[2-[1-[4-[1-(2-Methoxy)naphthyl]]-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder N-[2-[1-[4-[1-(5,6,7,8-Tetrahydro)-naphthyl]]piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamid oder (S)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder (R)-N-(1-Methyl-2-(4-(2-methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl]-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-chinolinyl)-cyclohexancarboxamid oder (rac)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder (S)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder (R)-N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-propyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(4-Phenyl-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Isopropylphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(4-pyridinyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(3-pyridyl)-cyclohexancarboxamid oder N-(2-(4-(2-Methoxyphenyl)-piperazin-1-yl)-ethyl)-N-(2-pyridinyl)-cyclohex-1-encarboxamid oder N-(2-(4-(2-Methoxyphenyl)-1-piperazinyl)-ethyl)-N-(2-pyridinyl)-cyclohexanthiocarboxamid oder ein pharmazeutisch annehmbares Salz hievon ist.

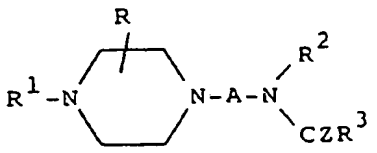
8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches das Vereinigen einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch annehmbaren Säureadditionssalzes hievon mit einem pharmazeutisch annehmbaren Träger umfaßt.

9. Verfahren nach Anspruch 1, wobei der aktive Bestandteil durch das Verfahren nach einem der Ansprüche 1 bis 7 hergestellt wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, IT, LI, LU, NL, PT, SE

1. Composé de formule générale :



(I)

ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci, dans lequel :

A est une chaîne alcoylène de 2 à 4 atomes de carbone, facultativement substituée par un ou plusieurs radicaux alcoyle inférieur;

Z est oxygène ou soufre;

R est hydrogène ou alcoyle inférieur;

R^1 est un radical aryle ou hétéroaryle, mono- ou bicyclique;

R^2 est un radical hétéroaryle mono- ou bicyclique, et

R^3 est hydrogène, alcoyle inférieur, cycloalcoyle, cycloalcényle, cycloalcoyl-(alcoyle inférieur), aryle, aryl(alcoyle inférieur), hétéroaryle, hétéroaryl(alcoyle inférieur), un radical de formule $-NR^4R^5$ - [dans lequel R^4 est hydrogène, alcoyle inférieur, aryle ou aryl(alcoyle inférieur) et R^5 est hydrogène, alcoyle inférieur, -CO(alcoyle inférieur), aryle, -COaryle, aryl(alcoyle inférieur), cycloalcoyle ou cycloalcoyl(alcoyle inférieur) ou R^4 t R^5 forment ensemble avec l'atome d'azote auquel ils sont fixés, un cycle hétérocyclique saturé qui peut contenir un autre hétéroatome] ou un radical de formule $-OR^6$ -

[où -R^6 est alcoyle inférieur, cycloalcoyle, cycloalcoyl(alcoyle inférieur), aryle, aryl(alcoyle inférieur), hétéroaryle ou hétéroaryl(alcoyle inférieur)].

2. Composé suivant la revendication 1, dans lequel A est -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$- ou -$CH(CH_3)$-CH_2-.

3. Composé suivant la revendication 1 ou 2, dans lequel R est hydrogène.

4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R^1 est o-méthoxyphényle, o-isopropylphényle, 4-fluoro-2-méthoxyphényle, 2,3-dihydro[1,4]-benzodioxann-5-yle, pyrimid-2-yle, 1-naphtyle, 3-(1,2-benzisothiazolyle), 1-(7-méthoxynaphtyle) ou 1-(5,6,7,8-tétrahydro)naphtyle.

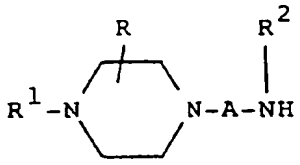
5. Composé suivant l'une quelconque des revendications 1 à 4, dans lequel R^2 est pyridyl-2-yle, quinoléin-2-yle ou thiazol-2-yle.

6. Composé suivant l'une quelconque des revendications 1 à 5, dans lequel R^3 est alcoyle inférieur, cycloalcoyle, cycloalcényle, phényle, pipéridino ou -NHcycloalcoyle.

7. Composé suivant la revendication 1, qui est le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou la N-cyclohexyl-N'-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)urée ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)benzamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)triméthylacétamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-thiazolyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(4-fluoro-2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)pipérazinyl]]éthyl]-N-(2-pyridinylcyclohexanecarboxamide ou le N-[2-[1-[4-[3-(1,2-benzisothiazolyl)]]pipérazinyl]éthyl]-N-(2-pyridyl)cyclohexanecarboxamide ou la N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(1-pipéridinylcarbonyl)-2-aminopyridine ou la N-[2-[4-(2-méthoxyphényl)-pipérazin-1-yl]éthyl]-N-(pyridin-2-yl)-N'-cyclohexylthiourée ou le N-[2-[4-(2-hydroxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(1-naphtyl)]pipérazinyl]éthyl]-N-(2-pyridyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(2-méthylphényl)]pipérazinyl]éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-(2-fluorophényl)]pipérazinyl]éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-(1-iso-quinoléinyl)]pipérazinyl]éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-[1-(7-méthoxy)naphtyl]]pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridyl)-adamantane-1-carboxamide ou le N-[2-[1-[4-[1-(2-méthoxy)naphtyl]]pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou leN-[2-[1-[4-[1-(5,6,7,8-tétrahydro)naphtyl]]pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le (S)-N-[1-méthyl-2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le (R)-N-[1-méthyl-2-[4-[2-méthoxyphényl)-1-pipérazinyl]-éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[3-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-quinoléinyl)cyclohexanecarboxamide ou le (rac)-N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le (S)-N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le (R)-N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl-N-(2-pyridyl)-cyclohexanecarboxamide ou le N-[2-(4-phényl-1-pipérazinyl)éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-isopropylphényl)-1-pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(4-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxy-phényl)-1-pipérazinyl]éthyl]-N-(3-pyridyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)pipérazin-1-yl]éthyl]-N-(2-pyridinyl)cyclohex-1-ènecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)-cyclohexanethiocarboxamide ou un sel pharmaceutiquement acceptable de ceux-ci.

8. Procédé de préparation d'un composé suivant la revendication 1, qui comprend :

(a) l'acylation d'un amine de formule (II) :

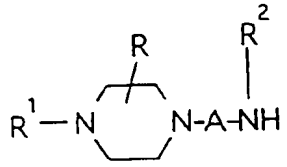


(II)

(où A, R, R^1 et R^2 ont les significations données à la revendication 1) avec un acide de formule (III) :

R^3CZOH (III)

(où Z et R^3 sont comme défini à la revendication 1) ou avec un dérivé acylant de celui-ci, ou
(b) la réaction d'une amine de formule (II) :

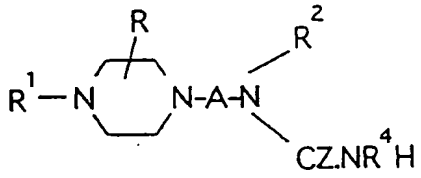


(II)

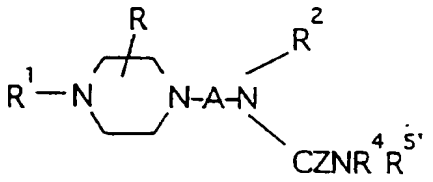
(où A, R, R^1 et R^2 sont comme défini à la revendication 1) avec un isocyanate ou un isothiocyanate de formule :

R^5NCZ

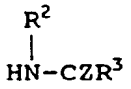
(où R^5 et Z sont comme défini à la revendication 1),
ou
(c) l'acylation d'un composé de formule :



(où R, R^1, R^2, R^4, A et Z sont comme défini dans la revendication 1) pour donner un composé de formule :

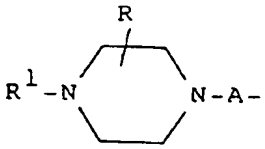


(où R, R^1, R^2, R^4, A et Z sont comme défini dans la revendication 1) et R^5 est -CO(alcoyle inférieur) ou -COaryle, ou
(d) l'acoylation d'un amide ou thioamide de formule (IV) :

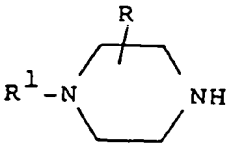


(IV)

(où R^2, R^3 et Z sont comme défini dans la revendication 1) avec un agent alcoylant muni du radical :



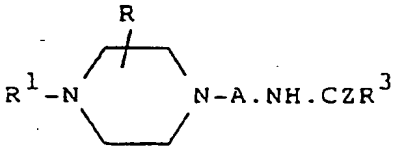
(où R, R^1 et A sont comme défini dans la revendication 1), ou
(e) l'acoylation d'un composé de formule :



(où R et R^1 sont comme défini dans la revendication 1) avec un composé de formule :

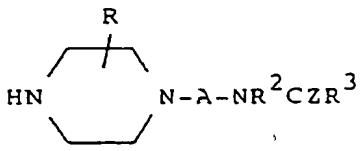
$X\text{-}A\text{-}NR^2\text{-}CZ\text{-}R^3$ (V)

(où A, R, R^1, R^2, R^3 et Z sont comme défini dans la revendication 1 et X est un groupe partant), ou
(f) l'héteroarylation d'un composé de formule :



(VI)

(où R, R^1, R^3, A et Z sont comme défini dans la revendication 1) avec un composé muni du radical hétéroaryle R^2 (où R^2 est comme défini dans la revendication 1), ou
(g) la réaction d'un composé de la pipérazine de formule :



(où R, R^2, R^3, A et Z sont comme défini dans la revendication 1) avec un composé du fluor de formule :

R^1F

où R^1 est un radical aryle ou hétéroaryle, mono-ou bicyclique qui est activé par rapport à la substitution nucléophile, ou
(h) la sulfuration d'un composé de formule (I) où Z est de l'oxygène pour donner un composé de formule (I) où Z est du soufre, ou
(i) la conversion d'une base suivant la revendication 1 en un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci, ou
(j) la conversion d'un sel d'addition d'acide pharmaceutiquement acceptable suivant la revendication 1 en une base libre.

9. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 7, en association avec un excipient pharmaceutiquement acceptable.

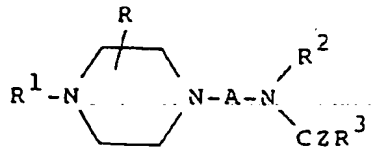
10. Composé suivant l'une quelconque des revendications 1 à 7, à utiliser comme produit pharmaceutique.

11. Composé suivant l'une quelconque des revendications 1 à 7, à utiliser comme anxiolytique, antidépresseur, hypotenseur ou agent pour la régulation du cycle sommeil/éveil, du comportement alimentaire et/ou des fonctions sexuelles.

12. 1-(2-Méthoxyphényl)-4-[2-(2-pyridinylamino)éthyl]pipérazine.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule générale :

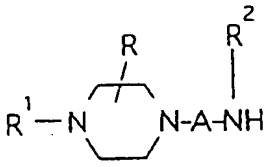


(I)

ou d'un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci, dans lequel :
A est une chaîne alcoylène de 2 à 4 atomes de carbone, facultativement substituée par un ou plusieurs radicaux alcoyle inférieur;
Z est oxygène ou soufre;
R est hydrogène ou alcoyle inférieur;
R^1 est un radical aryle ou hétéroaryle, mono- ou bicyclique;
R^2 est un radical hétéroaryle mono- ou bicyclique, et
R^3 est hydrogène, alcoyle inférieur, cycloalcoyle, cycloalcényle, cycloalcoyl(alcoyle inférieur), aryle,

aryl(alcoyle inférieur), hétéroaryle, hétéroaryl(alcoyle inférieur), un radical d formule $-NR^4R^5$ [dans lequel R^4 est hydrogène, alcoyle inférieur, aryle ou aryl(alcoyle inférieur) et R^5 est hydrogène, alcoyle inférieur, -CO(alcoyle inférieur), aryle, -COaryle, aryl(alcoyle inférieur), cycloalcoyle ou cycloalcoyl-(alcoyle inférieur) ou R^4 et R^5 forment ensemble avec l'atome d'azote auquel ils sont fixés un cycle hétérocyclique saturé qui peut contenir un autre hétéroatome] ou un radical de formule $-OR^6$ [où R^6 est alcoyle inférieur, cycloalcoyle, cycloalcoyl(alcoyle inférieur), aryle, aryl(alcoyle inférieur), hétéroaryle ou hétéroaryl(alcoyle inférieur)] qui comprend :

(a) l'acylation d'une amine de formule (II) :



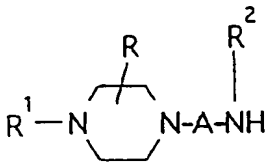
(II)

(où A, R, R^1 et R^2 ont les significations données ci-dessus) avec un acide de formule (III) :

R^3CZOH (III)

(où Z et R^3 sont comme défini ci-dessus) ou avec un dérivé acylant de celui-ci, ou

(b) la réaction d'une amine de formule (II) :



(II)

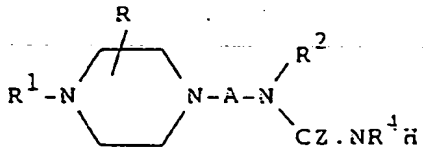
(où A, R, R^1 et R^2 sont comme défini ci-dessus) avec un isocyanate ou un isothiocyanate de formule :

R^5NCZ

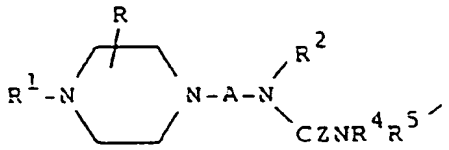
(où R^5 et Z sont comme défini ci-dessus),

ou

(c) l'acylation d'un composé de formule :

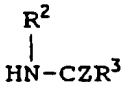


(où R, R^1, R^2, R^4, A et Z sont comme défini ci-dessus) pour donner un composé de formule :



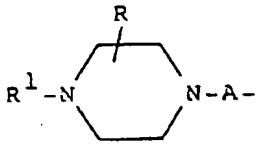
(où R, R^1, R^2, R^4, A et Z sont comme défini ci-dessus) et R^5 est -CO(alcoyle inférieur) ou -COaryle : ou

(d) l'acoylation d'un amide ou thioamide de formule (IV) :



(IV)

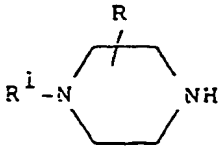
(où R^2, R^3 et Z sont comme défini ci-dessus) avec un agent alcoylant muni du radical :



(où R, R^1 et A sont comme définis ci-dessus),

ou

(e) l'acoylation d'un composé de formule :

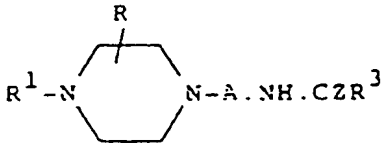


(où R et R^1 sont comme défini ci-dessus) avec un composé de formule :

$X\text{-}A\text{-}NR^2\text{-}CZ\text{-}R^3$ (V)

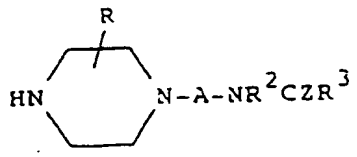
(où A, R, R^1, R^2, R^3 et Z sont comme défini ci-dessus et X est un groupe partant), ou

(f) l'hétéroarylation d'un composé de formule :



(VI)

(où R, R^1, R^3, A et Z sont comme défini ci-dessus) avec un composé muni du radical hétéroaryle R^2 (où R^2 est comme défini ci-dessus), ou
(g) la réaction d'un composé de la pipérazine de formule :



(où R, R^2, R^3, A et Z sont comme défini ci-dessus) avec un composé du fluor de formule :

R^1F

où R^1 est un radical aryle ou hétéroaryle, mono-ou bicyclique qui est activé par rapport à la substitution nucléophile, ou
(h) la sulfuration d'un composé de formule (I) où Z est de l'oxygène pour donner un composé de formule (I) où Z est du soufre, ou
(i) la conversion d'une base de formule (I) en un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci, ou
(j) la conversion d'un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule (I) en une base libre de celui-ci.

2. Procédé suivant la revendication 1, dans lequel A est $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ ou $-CH(CH_3)-CH_2-$.

3. Procédé suivant la revendication 1 ou 2, dans lequel R est hydrogène.

4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel R^1 est o-méthoxyphényl, o-isopropylphényle, 4-fluor-2-méthoxyphényle, 2,3-dihydro[1,4]-benzodioxann-5-yle, pyrimid-2-yle, 1-naphtyle, 3-(1,2-benzisothiazolyle), 1-(7-méthoxynaphtyle) ou 1-(5,6,7,8-tétrahydro)naphtyle.

5. Procédé suivant l'une quelconque des revendications 1 à 4, dans lequel R^2 est pyrid-2-yle, quinoléin-2-yle ou thiazol-2-yle.

6. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel R^3 est alcoyle inférieur, cycloalcoyle, cycloalcényle, phényle, pipéridino ou -NHcycloalcoyle.

7. Procédé suivant la revendication 1, dans lequel le produit est le N-[2-[1-[4-(2-méthoxyphényl)-pipérazinyl]]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou la N-cyclohexyl-N'-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)urée ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)benzamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)-triméthylacétamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-thiazolyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-(4-fluoro-2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[1-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)pipérazinyl]]éthyl]-N-(2-pyridinylcyclohexanecarboxamide ou le N-[2-[1-[4-[3-(1,2-benzisothiazolyl)]]pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou la N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(1-pipéridinylcarbonyl)-2-aminopyridine ou la N-[2-[4-(2-méthoxyphényl)pipérazin-1-yl]éthyl]-N-(pyridin-2-yl)-N'-cyclohexylthiourée ou le N-[2-[4-(2-hydroxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamideou leN-[2-[1-[4-(1-naphtyl)]pipérazinyl]éthyl]-N-(2-pyridyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(2-méthylphényl)]pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamideou le N-[2-[1-[4-(2-fluorophényl)]-pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(1-isoquinoléinyl)]pipérazinyl]-éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[1-[4-[1-(7-méthoxy)naphtyl]]pipérazinyl]éthyl]-N-(2-pyridyl)cyclohexanecarboxamide ou le N-[2-[1-[4-(2-méthoxyphényl)pipérazinyl]]éthyl]-N-(2-pyridyl)adamantane-1-carboxamide ou le N-[2-[1-[4-[1-(2-méthoxy)naphtyl]]pipérazinyl]éthyl]-N-(2-pyridyl)cyclohexanecarboxamide ou le N-[2-[1-[4-[1-(5,6,7,8-tétrahydro)naphtyl]]pipérazinyl]éthyl]-N-(2-pyri-

dyl)cyclohexanecarboxamide ou le (S)-N-[1-méthyl-2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le (R)-N-[1-méthyl-2-[4-[2-méthoxyphényl)-1-pipérazinyl]-éthyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[3-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl]-N-(2-pyridinyl)cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-quinoléinyl)-cyclohexanecarboxamide ou le (rac)-N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le (S)-N-[2-[4-(2-méthoxyphényl)-1-piperazinyl]propyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le (R)-N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]propyl-N-(2-pyridyl)-cyclohexanecarboxamide ou le N-[2-(4-phényl-1-pipérazinyl)éthyl]-N-(2-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-isopropylphényl)-1-pipérazinyl]éthyl]-N-(2-pyridyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(4-pyridinyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(3-pyridyl)-cyclohexanecarboxamide ou le N-[2-[4-(2-méthoxyphényl)pipérazin-1-yl]éthyl]-N-(2-pyridinyl)cyclohex-1-ènecarboxamide ou le N-[2-[4-(2-méthoxyphényl)-1-pipérazinyl]éthyl]-N-(2-pyridinyl)-cyclohexanethiocarboxamide ou un sel pharmaceutiquement acceptable de ceux-ci.

8. Procédé de préparation d'une composition pharmaceutique qui comprend la mise en association d'un composé de formule (I) comme défini dans la revendication 1 ou d'un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci avec un excipient pharmaceutiquement acceptable.

9. Procédé suivant la revendication 1, dans lequel l'ingrédient actif est préparé par le procédé suivant l'une quelconque des revendications 1 à 7.